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International application number: PCT/GB05/001050

International filing date: 21 March 2005 (21.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: GB
Number: 0406280.8
Filing date: 19 March 2004 (19.03.2004)

Date of receipt at the International Bureau: 02 May 2005 (02.05.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



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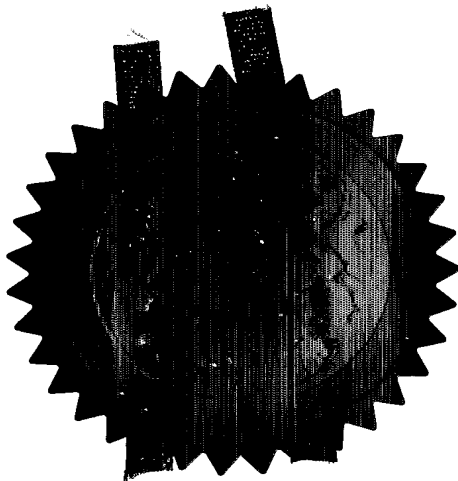
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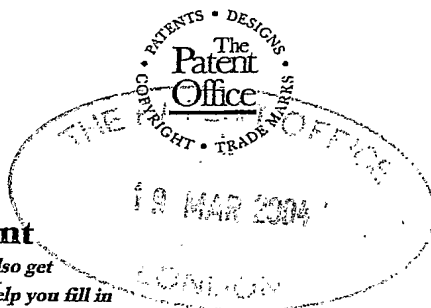
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100

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1. Your reference

P.91258 RCS

2. Patent application number

(The Patent Office will fill this part in)

0406280.8

19 MAR 2004

3. Full name, address and postcode of the or of each applicant (underline all surnames)

ARROW THERAPEUTICS LIMITED
Britannia House
7 Trinity Street
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Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

7708217002
United Kingdom

4. Title of the invention

CHEMICAL COMPOUNDS

5. Name of your agent (if you have one)

J. A. KEMP & CO.

"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)

14 South Square
Gray's Inn
London
WC1R 5JJ

Patents ADP number (if you know it)

26001

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

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Priority application number
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Date of filing
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7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note d)

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Patents Form 1/77

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Continuation sheets of this form

Description	59
Claim(s)	11 
Abstract	1
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10. If you are also filing any of the following, state how many against each item.

Priority documents	-
Translations of priority documents	-
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	-
Request for a preliminary examination and search (Patents Form 9/77)	-
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Signature(s)

J.A. KEMP & CO.

Date 19 March 2004

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

SRINIVASAN, Ravi Chandran
020 7405 3292

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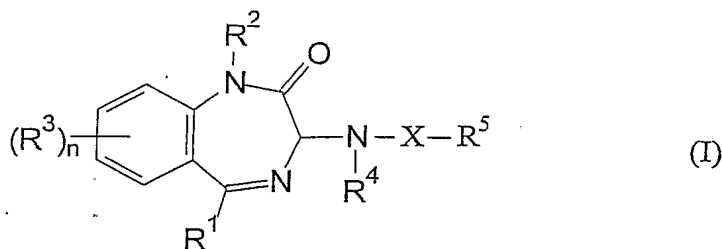
The present invention relates to a series of benzodiazepine derivatives which
5 are active against Respiratory Syncytial Virus (RSV).

RSV is a major cause of respiratory illness in patients of all ages. In adults, it tends to cause mild cold symptoms. In school-aged children, it can cause a cold and bronchial cough. In infants and toddlers it can cause bronchiolitis (inflammation of the smaller airways of the lungs) or pneumonia. It has also been found to be a
10 frequent cause of middle ear infections (otitis media) in pre-school children. RSV infection in the first year of life has been implicated in the development of asthma during childhood.

Current anti-RSV therapy involves the use of a monoclonal antibody to RSV, called palivizumab. Such use of palivizumab is a prophylactic, rather than
15 therapeutic, treatment of RSV. However, although this antibody is often effective, it is expensive. Indeed, its expense means that it is unavailable for many people in need of anti-RSV therapy. There is therefore an urgent need for effective alternatives to existing anti-RSV therapy.

It has now surprisingly been found that the particular benzodiazepine
20 derivatives of the general formula (I) set out below are active against RSV.

Accordingly, the present invention provides, in a first embodiment, the use of a compound which is (a) a benzodiazepine derivative of formula (I) or an N-oxide thereof, or (b) a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in treating or preventing an RSV infection



25 wherein:

- R¹ represents C₁₋₆ alkyl, aryl or heteroaryl;

- R^2 represents hydrogen or C_{1-6} alkyl;
 - each R^3 is the same or different and represents halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, amino, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro, cyano, $-CO_2R'$, $-CONR'R''$, $-NH-CO-R'$, $-S(O)R'$, $-S(O)_2R'$, $-NH-S(O)_2R'$, $-S(O)NR'R''$ or $-S(O)_2NR'R''$, wherein each R' and R'' is the same or different and represents hydrogen or C_{1-6} alkyl;
 - n is from 0 to 3;
 - R^4 represents hydrogen or C_{1-6} alkyl;
 - X represents $-CO-$, $-CO-NR'$, $-S(O)-$ or $-S(O)_2-$, wherein R' is hydrogen or a C_1-C_6 alkyl group; and
 - R^5 represents an aryl, heteroaryl or heterocyclyl group, which group is substituted by a C_1-C_6 hydroxyalkyl group or a $-(C_1-C_4 \text{ alkyl})-X_1-(C_1-C_4 \text{ alkyl})-X_2-(C_1-C_4 \text{ alkyl})$ group, wherein X_1 represents $-O-$, $-S-$ or $-NR'$, wherein R' represents H or a C_1-C_4 alkyl group, and X_2 represents $-CO-$, $-SO-$ or $-SO_2-$, or R_5 represents $-A_1-Y-A_2$, wherein:
 - A_1 is an aryl, heteroaryl, carbocyclyl or heterocyclyl group;
 - Y represents a direct bond or a C_1-C_4 alkylene, $-SO_2-$, $-CO-$, $-O-$, $-S-$ or $-NR'$ moiety, wherein R' is a C_1-C_6 alkyl group; and
 - A_2 is an aryl, heteroaryl, carbocyclyl or heterocyclyl group.
- As used herein, a C_{1-6} alkyl group or moiety is a linear or branched alkyl group or moiety containing from 1 to 6 carbon atoms, such as a C_{1-4} alkyl group or moiety. Examples of C_{1-4} alkyl groups and moieties include methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl and *t*-butyl. For the avoidance of doubt, where two alkyl moieties are present in a group, the alkyl moieties may be the same or different.
- As used herein, a hydroxyalkyl group is typically a said alkyl group that is substituted by one or more hydroxy groups. Typically, it is substituted by one, two or three hydroxy groups. Preferably, it is substituted by a single hydroxy group. A preferred hydroxyalkyl group is $-CH_2-OH$.
- As used herein, an acyl group is a C_{2-7} acyl group, for example a group $-CO-R$, wherein R is a said C_{1-6} alkyl group.
- As used herein, an aryl group is typically a C_{6-10} aryl group such as phenyl or naphthyl. Phenyl is preferred. An aryl group may be unsubstituted or substituted at

any position. Typically, it carries 0, 1, 2 or 3 substituents.

Suitable substituents on an aryl group include halogen, C₁₋₆ alkyl, C₂₋₇ acyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, nitro, cyano, carbamoyl, mono(C₁₋₆ alkyl)carbamoyl, di(C₁₋₆ alkyl)carbamoyl, amino, 5 mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, -CO₂R', -CONR'R'', -S(O)R', -S(O)₂R', -S(O)NR'R'', -S(O)₂NR'R'' -NH-S(O)₂R' or -NH-CO-R', wherein each R' and R'' is the same or different and represents hydrogen or C₁₋₆ alkyl.

Preferred substituents on an aryl group include halogen, C₁₋₆ alkyl, C₂₋₇ acyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, amino, 10 mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro, cyano, -CO₂R', -S(O)R', -S(O)₂R' and -S(O)₂NR'R'', wherein each R' and R'' is the same or different and represents hydrogen or C₁₋₄ alkyl.

Particularly preferred substituents include fluorine, chlorine, bromine, iodine, cyano, C₁₋₄ alkyl, C₂₋₄ acyl, hydroxy, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ haloalkyl, C₁₋₄ 15 haloalkoxy, amino, mono(C₁₋₄ alkyl)amino, di(C₁₋₄ alkyl)amino, nitro, -CO₂R', -S(O)₂R' and -S(O)₂NH₂, wherein R' represents C₁₋₂ alkyl. Most preferred substituents are chlorine, fluorine, cyano, C_{1-C4} alkyl and C_{1-C4} haloalkyl substituents.

As used herein, references to an aryl group include fused ring systems in 20 which an aryl group is fused to a monocyclic carbocyclyl, heterocyclyl or heteroaryl group or to a fused group which is a monocyclic carbocyclyl, heterocyclyl or heteroaryl group which is fused to a phenyl ring. Typically, said fused ring systems are systems in which an aryl group is fused to a monocyclic carbocyclyl, heterocyclyl or heteroaryl group.

25 Preferred such fused ring systems are those wherein an aryl group is fused to a monocyclic heterocyclyl or heteroaryl group or to a monocyclic carbocyclic group fused to a phenyl ring, in particular those wherein an aryl group is fused to a heterocyclyl or heteroaryl group. Examples of such fused ring systems are groups in which a phenyl ring is fused to a thienyl group or to a tetrahydrofuranyl group to 30 form a benzothienyl or dihydrobenzofuranyl group. Further examples of such fused rings are groups in which a phenyl ring is fused to a dioxanyl group, a pyrrolyl group or a 2,3-dihydroinden-1-one group to form a benzodioxinyl, indolyl or a 9H-fluoren-

9-one group. Most preferably, however, an aryl group, as used herein, is not fused to a monocyclic carbocyclyl, heterocyclyl or heteroaryl group or to a said fused group.

As used herein, a carbocyclyl group is a non-aromatic saturated or unsaturated monocyclic hydrocarbon ring, typically having from 3 to 6 carbon atoms.

5 Preferably it is a saturated hydrocarbon ring (i.e. a cycloalkyl group) having from 3 to 6 carbon atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. It is preferably cyclopropyl, cyclopentyl or cyclohexyl, most preferably cyclopropyl. A cycloalkyl group may be unsubstituted or substituted at any position. Typically, it carries 0, 1, 2 or 3 substituents.

10 Suitable substituents on a carbocyclyl group include halogen, C₁₋₆ alkyl, C₂₋₇ acyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, nitro, cyano, carbamoyl, mono(C₁₋₆ alkyl)carbamoyl, di(C₁₋₆ alkyl)carbamoyl, amino, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, oxo, -CO₂R', -CONR'R'', -S(O)R', -S(O)₂R', -S(O)NR'R'', -S(O)₂NR'R'', -NH-S(O)₂R' or -NH-CO-R', wherein each R' and R'' is the same or different and represents hydrogen or C₁₋₆ alkyl.

15 Preferred substituents on an carbocyclyl group include halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro, cyano and oxo. Particularly preferred substituents include fluorine, chlorine, bromine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, nitro and oxo.

20 Most preferably, a carbocyclyl group is unsubstituted.

As used herein, a heterocyclyl group is a non-aromatic saturated or unsaturated carbocyclic ring, typically having from 5 to 10 carbon atoms, in which one or more, for example 1, 2 or 3, of the carbon atoms is replaced by a heteroatom selected from N, O and S. Saturated heterocyclyl groups are preferred. Examples

25 include tetrahydrofuranyl, tetrahydrothienyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, dioxolanyl, thiazolidinyl, tetrahydropyranyl, piperidinyl, dioxanyl, piperazinyl, morpholinyl, thiomorpholinyl and thioxanyl. Further examples include dithiolanyl, oxazolidinyl, tetrahydrothiopyranyl and dithianyl. Piperazinyl, piperidinyl, thiomorpholinyl, imidazolidinyl and morpholinyl groups are preferred.

30 As used herein, references to a heterocyclyl group include fused ring systems in which a heterocyclyl group is fused to a phenyl group. Preferred such fused ring systems are those wherein a 5- to 6-membered heterocyclyl group is fused to a

phenyl group. An example of such a fused ring system is a group wherein a 1H-imidazol-2(3H)-onyl group or a imidazolidin-2-onyl group is fused to a phenyl ring or a pyridine ring, to form, for example, a 1H-benzo[d]imidazol-2(3H)-onyl group or a 1H-imidazo[4,5-b]pyridin-2(3H)-one group. Most preferably, however, a

5 heterocyclcyl group is monocyclic.

A heterocyclic group may be unsubstituted or substituted at any position. Typically, it carries 0, 1 or 2 substituents.

Suitable substituents on a heterocyclcyl group include halogen, C₁₋₆ alkyl, C₂₋₇ acyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, nitro,
10 cyano, carbamoyl, mono(C₁₋₆ alkyl)carbamoyl, di(C₁₋₆ alkyl)carbomyl, amino, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, oxo, -CO₂R', -CONR'R'', -S(O)R', -S(O)₂R', -S(O)NR'R'', -S(O)₂NR'R'', -NH-S(O)₂R' or -NH-CO-R', wherein each R' and R'' is the same or different and represents hydrogen or C₁₋₆ alkyl.

Preferred substituents on a heterocyclcyl group include halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, mono(C₁₋₆ alkyl)amino,
15 di(C₁₋₆ alkyl)amino, nitro, cyano and oxo. Particularly preferred substituents include fluorine, chlorine, bromine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl, nitro and oxo. Most preferably, a heterocyclcyl group is unsubstituted or substituted by one or two C₁₋₂ alkyl or oxo groups. An example of a substituted heterocyclic group is S,S-dioxo-thiomorpholino.
20

As used herein, a halogen is typically chlorine, fluorine, bromine or iodine. It is preferably chlorine, fluorine or bromine. It is more preferably chlorine or fluorine.

As used herein, an alkoxy group is typically a said alkyl group attached to an oxygen atom. An alkylthio group is typically a said alkyl group attached to a thio
25 group. A haloalkyl or haloalkoxy group is typically a said alkyl or alkoxy group substituted by one or more said halogen atoms. Typically, it is substituted by 1, 2 or 3 said halogen atoms. Preferred haloalkyl and haloalkoxy groups include perhaloalkyl and perhaloalkoxy groups such as -CX₃ and -OCX₃ wherein X is a said halogen atom, for example chlorine or fluorine. Particularly preferred haloalkyl
30 groups are -CF₃ and -CCl₃. Particularly preferred haloalkoxy groups are -OCF₃ and -OCCl₃.

As used herein, a heteroaryl group is typically a 5- to 10-membered aromatic

ring, such as a 5- or 6-membered ring, containing at least one heteroatom, for example 1, 2 or 3 heteroatoms, selected from O, S and N. Examples include pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, furanyl, thienyl, pyrazolidinyl, pyrrolyl, oxadiazolyl, isoxazolyl, thiadiazolyl, thiazolyl, imidazolyl and pyrazolyl groups.

5 Further examples include oxazolyl and isothiazolyl. Preferred heteroaryl groups are pyridyl, thienyl, oxazolyl, isoxazolyl, thiazolyl, furanyl and pyrazolyl.

As used herein, references to a heteroaryl group include fused ring systems in which a heteroaryl group is fused to a phenyl group or to a monocyclic heterocyclyl group. Preferred such fused ring systems are those wherein a 5- to 6-membered
10 heteroaryl group is fused to a phenyl group or to a 5- to 6- membered heterocyclyl group. Examples of such fused ring systems are benzofuranyl, benzothiophenyl, indolyl, benzimidazolyl, benzoxazolyl, quinolinyl, quinazolinyl, isoquinolinyl and 1H-imidazo[4,5-b]pyridin-2(3H)-one moieties. Most preferably, said fused ring system is a 1H-imidazo[4,5-b]pyridin-2(3H)-one moiety.

15 A heteroaryl group may be unsubstituted or substituted at any position. Typically, it carries 0, 1, 2 or 3 substituents.

Suitable substituents on a heteroaryl group include halogen, C₁₋₆ alkyl, C₂₋₇ acyl, hydroxy, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, nitro, cyano, carbamoyl, mono(C₁₋₆ alkyl)carbamoyl, di(C₁₋₆ alkyl)carbamoyl, amino,
20 mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, -CO₂R', -CONR'R'', -S(O)R', -S(O)₂R', -S(O)NR'R'', -S(O)₂NR'R'', -NH-S(O)₂R' or -NH-CO-R', wherein each R' and R'' is the same or different and represents hydrogen or C₁₋₆ alkyl.

Preferred substituents on a heteroaryl group include halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro and cyano. Particularly preferred substituents include fluorine,
25 chlorine, bromine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ haloalkyl and nitro. Most preferred substituents include fluorine, chlorine, bromine, C₁₋₂ alkyl and C₁₋₂ haloalkyl substituents.

When R¹ is an aryl or heteroaryl group it is typically unsubstituted or
30 substituted by one, two or three substituents selected from halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl or C₁₋₆ haloalkoxy. Preferably, it is unsubstituted or substituted by one or two substituents selected from fluorine,

chlorine, bromine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ haloalkyl or C₁₋₄ haloalkoxy. More preferably, it is unsubstituted or substituted by a single fluorine, chlorine, C₁₋₂ alkyl, C₁₋₂ alkoxy, C₁₋₂ alkylthio, C₁₋₂ haloalkyl or C₁₋₂ haloalkoxy substituent.

- 5 Typically, R¹ is C₁₋₆ alkyl or aryl. Preferably, R¹ is C₁₋₂ alkyl or aryl. More preferably, R¹ is C₁₋₂ alkyl or phenyl. More preferably, R¹ is an unsubstituted phenyl group.

Typically, R² is hydrogen or C₁₋₄ alkyl. Preferably, R² is hydrogen.

- 10 Typically, R³ is halogen, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, amino, mono(C₁₋₄ alkyl)amino or di(C₁₋₄ alkyl)amino. Preferably, R³ is fluorine, chlorine, bromine, C₁₋₂ alkyl, C₁₋₂ alkoxy, C₁₋₂ alkylthio, C₁₋₂ haloalkyl, C₁₋₂ haloalkoxy, amino, mono(C₁₋₂ alkyl)amino or di(C₁₋₂ alkyl)amino. More preferably, R³ is methyl, trifluoromethyl, fluorine, chlorine or bromine. Most preferably, R³ is methyl or chlorine.

- 15 Typically, n is 0, 1 or 2. Preferably, n is 0 or 1. Most preferably, n is 0.

Typically, R⁴ is hydrogen or C₁₋₄ alkyl. Preferably, R⁴ is hydrogen or C₁₋₂ alkyl. More preferably, R⁴ is hydrogen or methyl. Most preferably, R⁴ is hydrogen

Typically, X is -CO-, -S(O)₂- or -CO-NR', wherein R' represents hydrogen or a C₁₋₂ alkyl group. Preferably, X is -CO- or -CO-NR'.

- 20 When R⁵ is a heterocyclyl or heterocyclyl group which is substituted by a C₁₋₆ hydroxyalkyl group or a -(C₁₋₄ alkyl)-X₁-(C₁₋₄ alkyl)-X₂-(C₁₋₄ alkyl) group, the heterocyclyl or heteroaryl group is typically a 5- or 6- membered ring.

Preferably, it is a 5- or 6- membered heteroaryl group, for example a furanyl group.

- 25 Typically, the C₁₋₆ hydroxyalkyl group is a -CH₂-OH group. Typically, X₁ is -NR', wherein R' is hydrogen or C₁₋₂ alkyl. Typically, X₂ is -S(O)₂-.

- Typically, A₁ is an aryl or heteroaryl group. Preferably, A₁ is a monocyclic aryl or heteroaryl group, a naphthyl group or a heteroaryl group fused to a monocyclic oxo substituted heterocyclyl group. More preferably, A₁ is a phenyl group, a monocyclic 5- or 6- membered heteroaryl group or a 5- to 6- membered heteroaryl group fused to a monocyclic oxo substituted 5- to 6- membered heterocyclyl group (for example an oxo substituted imidazolidine group). Most preferably, A₁ is a phenyl, pyridyl, furanyl, thiazolyl, oxazolyl, isoxazolyl, thienyl or
- 30

1H-imidazo[4,5-b]pyridin-2-(3H)-one moiety.

Typically, the moiety A₁ is unsubstituted or substituted by 1 or 2 substituents selected from halogen, cyano, nitro, C₁-C₄ alkyl, C₁-C₄ haloalkyl and C₁-C₄ alkoxy substituents. Preferably, the substituents are selected from halogen, cyano, C₁-C₂ alkyl, C₁-C₂ haloalkyl and C₁-C₂ alkoxy substituents.

Typically, Y represents a direct bond, a C₁-C₂ alkylene group, -SO₂- or -O-.

Typically, A₂ is a phenyl, 5- to 6- membered heteroaryl, 5- to 6- membered heterocyclyl or C₃-C₆ cycloalkyl group. Preferably, A₂ is a piperazinyl, pyridyl, morpholinyl, thiomorpholinyl, pyrrolidinyl, piperidinyl, pyrazinyl, cyclopropyl or phenyl group.

Typically, when A₂ is a heterocyclyl group it is attached to the moiety Y via a N atom.

Typically, the moiety A₂ is unsubstituted or substituted by one or two substituents which are selected from C₁-C₄ alkyl and halogen substituents when A₂ is a heteroaryl or aryl group and which are selected from C₁-C₄ alkyl, halogen and oxo substituents when A₂ is a carbocyclic or heterocyclyl group.

Most preferably, A₂ is a piperazinyl, pyridyl, morpholinyl, pyrrolidinyl, piperidinyl, pyrazinyl, cyclopropyl, phenyl or S,S-dioxo-thiomorpholino group, which group is unsubstituted or is substituted by a C₁-C₂ alkyl group.

Preferred compounds of the invention are those in which:

- R¹ is C₁₋₆ alkyl or aryl;
- R² is hydrogen or C₁₋₄ alkyl;
- R³ is halogen, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, amino, mono(C₁₋₄ alkyl)amino or di(C₁₋₄ alkyl)amino or, preferably,
- 25 R³ is fluorine, chlorine, bromine, C₁₋₂ alkyl, C₁₋₂ alkoxy, C₁₋₂ alkylthio, C₁₋₂ haloalkyl, C₁₋₂ haloalkoxy, amino, mono(C₁₋₂ alkyl)amino or di (C₁₋₂ alkyl)amino;
- n is 0, 1 or 2;
- R⁴ is hydrogen or C₁₋₄ alkyl;
- X is -CO-, -CO-NR' or -S(O)₂-, wherein R' is hydrogen or a C₁-C₂ alkyl
- 30 group; and
- R⁵ is a 5- or 6- membered heterocyclyl or heteroaryl ring which is substituted by a C₁-C₆ hydroxyalkyl group or a -(C₁-C₄ alkyl)-X₁-(C₁-C₄ alkyl)-X₂-

(C₁-C₄ alkyl) group, wherein X₁ and X₂ are as defined above, or R⁵ represents -A₁-Y-A₂, wherein:

- A₁ is an aryl or heteroaryl group;
- Y is a direct bond, a C₁-C₂ alkylene group, -SO₂- or -O-; and
- 5 - A₂ is an aryl, heteroaryl, heterocyclyl or carbocyclyl group,
the aryl moiety in the R¹ group being unsubstituted or substituted by 1, 2 or 3 substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ alkylthio, C₁-C₆ haloalkyl and C₁-C₆ haloalkoxy groups,

the A₁ moiety being unsubstituted or substituted by 1 or 2 substituents
10 selected from halogen, cyano, nitro, C₁-C₄ alkyl, C₁-C₄ haloalkyl and C₁-C₄ alkoxy substituents; and

the A₂ moiety being unsubstituted or substituted by one or two substituents which are selected from C₁-C₄ alkyl and halogen substituents when A₂ is a heteroaryl or aryl group and which are selected from C₁-C₄ alkyl, halogen and oxo substituents
15 when A₂ is a carbocyclic or heterocyclyl group.

Further preferred compounds of the invention are those wherein:

- R¹ is C₁₋₂ alkyl or phenyl;
- R² is hydrogen or C₁₋₄ alkyl;
- R³ is methyl, trifluoromethyl, fluorine, chlorine or bromine;
- 20 - n is 0 or 1;
- R⁴ is hydrogen or C₁₋₂ alkyl;
- X is -CO-, -CO-NR'- or -S(O)₂, wherein R' is hydrogen or a C₁-C₂ alkyl group; and
- R⁵ is a 5- or 6- membered heterocyclyl or heteroaryl group which is
25 substituted by a C₁-C₆ hydroxyalkyl group or a -(C₁-C₄ alkyl)-NR'-(C₁-C₄ alkyl)-SO₂-(C₁-C₄ alkyl) group, wherein R' is hydrogen or C₁-C₂ alkyl, or R⁵ represents -A₁-Y-A₂, wherein:
- A₁ is a phenyl group, a monocyclic 5- or 6- membered heteroaryl group or a 5- or 6- membered heteroaryl group fused to a monocyclic oxo-substituted 5- to 6-
30 membered heterocyclyl group;
- Y represents a direct bond, a C₁-C₂ alkylene moiety, -SO₂- or -O-; and
- A₂ is a phenyl, 5- to 6- membered heteroaryl, 5- to 6- membered heterocyclyl

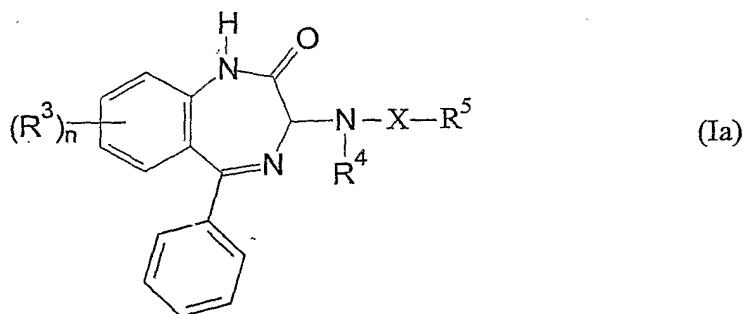
or C₃-C₆ cycloalkyl group,

the phenyl moiety in the R¹ group being unsubstituted or substituted by one or two substituents selected from fluorine, chlorine, bromine, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ haloalkyl or C₁₋₄ haloalkoxy;

5 the A₁ moiety being unsubstituted or substituted by 1 or 2 substituents selected from halogen, cyano, nitro, C₁-C₄ alkyl, C₁-C₄ haloalkyl and C₁-C₄ alkoxy substituents; and

the A₂ moiety being unsubstituted or substituted by 1 or 2 substituents which are selected from C₁-C₄ alkyl, halogen and oxo substituents when A₂ is a
10 heterocyclyl or cycloalkyl group and which are selected from C₁-C₄ alkyl and halogen substituents when A₂ is a phenyl or heteroaryl group.

Particularly preferred compounds of the invention are compounds of formula (Ia) and pharmaceutically acceptable salts thereof



15

wherein:

- X is -CO- or -CO-NH-; and
- R⁵ is a 5- to 6- membered heteroaryl group, for example a furanyl group,
20 which is substituted by -CH₂-OH or -(C₁-C₄ alkyl)-N(CH₃)-(C₁-C₄ alkyl)-SO₂-(C₁-C₄ alkyl) or R₅ represents -A₁-Y-A₂, wherein:
 - A₁ is a phenyl, pyridyl, furanyl, thiazolyl, oxazolyl, isoxazolyl, thienyl or 1H-imidazo[4,5-b]pyridin-2-(3H)-one moiety, which is unsubstituted or substituted by 1 or 2 substituents selected from halogen, cyano, C₁-C₂ alkyl, C₁-C₂ haloalkyl and
25 C₁-C₂ alkoxy substituents;
 - Y is a direct bond, a C₁-C₂ alkylene group, -SO₂- or -O-; and
 - A₂ is a piperazinyl, pyridyl, morpholinyl, pyrrolidinyl, piperidinyl, pyrazinyl,

cyclopropyl, phenyl or S,S-dioxo-thiomorpholino group, which is unsubstituted or substituted by a C₁-C₂ alkyl group.

Compounds of the formula (I) containing one or more chiral centre may be used in enantiomerically or diastereoisomerically pure form, or in the form of a mixture of isomers. For the avoidance of doubt, the chemical structures depicted herein are intended to embrace all stereoisomers of the compounds shown, including racemic and non-racemic mixtures and pure enantiomers and/or diastereoisomers.

Preferred compounds of the invention are optically active isomers. Thus, for example, preferred compounds of formula (I) containing only one chiral centre include an R enantiomer in substantially pure form, an S enantiomer in substantially pure form and enantiomeric mixtures which contain an excess of the R enantiomer or an excess of the S enantiomer. For the avoidance of doubt, the compounds of the formula (I) can, if desired, be used in the form of solvates.

As used herein, a pharmaceutically acceptable salt is a salt with a pharmaceutically acceptable acid or base. Pharmaceutically acceptable acids include both inorganic acids such as hydrochloric, sulphuric, phosphoric, diphosphoric, hydrobromic or nitric acid and organic acids such as citric, fumaric, maleic, malic, ascorbic, succinic, tartaric, benzoic, acetic, methanesulphonic, ethanesulphonic, benzenesulphonic or p-toluenesulphonic acid. Pharmaceutical acceptable bases include alkali metal (e.g. sodium or potassium) and alkaline earth metal (e.g. calcium or magnesium) hydroxides and organic bases such as alkyl amines, aralkyl amines or heterocyclic amines.

Particularly preferred compounds of the invention include:

- 6-(4-Methyl-piperazin-1-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-nicotinamide;
- 3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
- (S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
- (S)-2-Chloro-4-morpholin-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
- (S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-4-fluoro-(2-oxo-5-phenyl-2,3-dihydro-

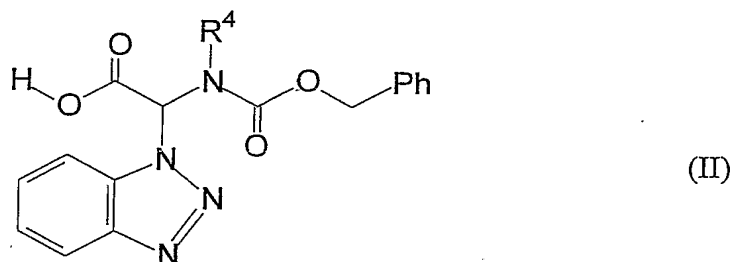
- 1H-benzo[e][1,4]diazepin-3-yl-benzamide;
- (S)-5-Chloro-2-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
- (S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-5-fluoro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
- 5 (S)-5-(4-Methyl-piperazin-1-ylmethyl)-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
- (S)-5-Pyrrolidin-1-ylmethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
- 10 (S)-5-Piperidin-1-ylmethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
- (S)-5-Dimethylaminomethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
- (S)-4-Fluoro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-piperidin-1-yl-benzamide;
- 15 (S)-4-Fluoro-2-morpholino-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
- (S)-4-Cyano-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-pyrrolidin-1-yl-benzamide;
- 20 (S)-4-Cyano-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-piperidine-1-yl-benzamide;
- (S)-N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-pyrrolidin-1-yl-4-trifluoromethyl-benzamide;
- (S)-N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-piperidin-1-yl-4-trifluoromethyl-benzamide;
- 25 (S)-2-Morpholin-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-4-trifluoromethyl-benzamide;
- (S)-N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-pyrrolidin-1-yl-5-trifluoromethyl-benzamide;
- 30 (S)-2-Morpholin-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-trifluoromethyl-benzamide;
- (S)-2-Morpholin-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-

- yl)-nicotinamide;
- (S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-nicotinamide;
- (S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-3-methyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
- (S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-4-methyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
- (S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-6-methyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
- 10 (S)-2-Chloro-6-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
- (S)-3-Cyclopropyl-2-oxo-2,3-dihydro-imidazo[4,5-b]pyridine-1-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
- (S)-3-(4-Methyl-piperazine-1-sulfonyl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
- 15 (S)-4-(4-Methyl-piperazin-1-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
- (S)-N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-(piperidine-1-sulfonyl)-benzamide;
- 20 (S)-3-(Morpholine-4-sulfonyl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
- (S)-5-Morpholin-4-ylmethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
- (S)-5-Hydroxymethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
- 25 (S)-5-(1,1-Dioxo-1λ6-thiomorpholin-4-ylmethyl)-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
- (S)-2-Chloro-4-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
- 30 (S)-2-Chloro-5-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
- (S)-5-{[(2-Methanesulfonyl-ethyl)-methyl-amino]-methyl}-furan-2-carboxylic acid

- (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 (S)-2-Pyridin-3-yl-thiazole-4-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 (S)-2-Pyridin-4-yl-thiazole-4-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 5 (S)-4-Methyl-2-pyrazin-2-yl-thiazole-5-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 (S)-2-Morpholin-4-ylmethyl-furan-3-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 10 (S)-3-Morpholin-4-ylmethyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
 (S)-5-Morpholin-4-ylmethyl-isoxazole-3-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 (S)-3-Morpholin-4-ylmethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 15 (S)-5-Pyridin-2-yl-thiophene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 (S)-2-Methyl-4-(morpholin-4-sulfonyl)-furan-3-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 20 (S)-6-Morpholin-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-nicotinamide;
 (S)-3-Morpholin-4-ylmethyl-thiophene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 (S)-5-Morpholin-4-ylmethyl-thiophene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 25 2-Morpholin-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
 (S)-5-Phenyl-oxazole-4-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 30 1-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-(4-phenoxyphenyl)-urea;
 an N-oxide of any of the above compounds;

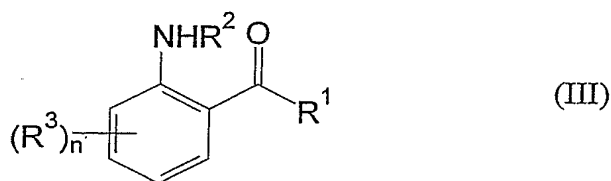
and pharmaceutically acceptable salts thereof.

Compounds of formula (I) may be prepared by reacting glyoxylic acid ($\text{HCO}-\text{CO}_2\text{H}$), benzotriazole and an appropriate benzyl carbamate at reflux in toluene, under Dean-Stark conditions giving the key protected amino acid of formula (II)

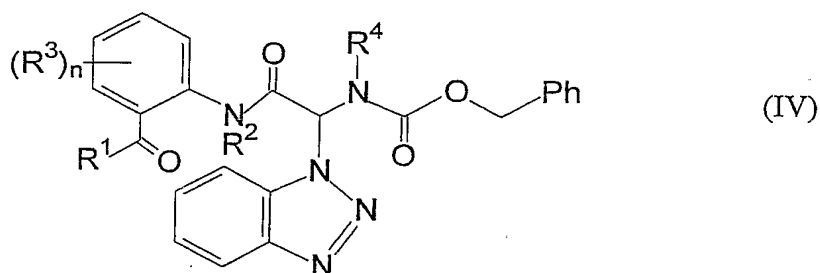


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The thus obtained amino acid of formula (II) can then be reacted with a suitable chlorinating agent, such as oxalyl chloride, followed by reaction with a 2-aminobenzophenone of formula (III)



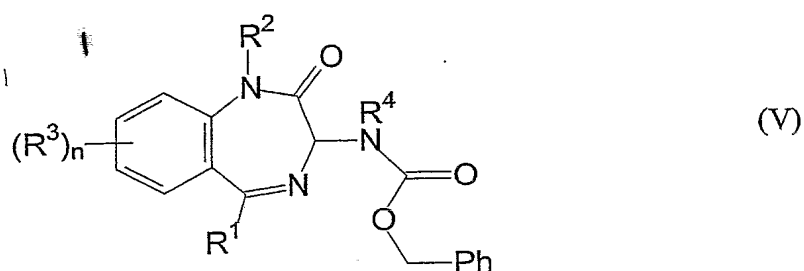
10 to give the intermediate amide of formula (IV)



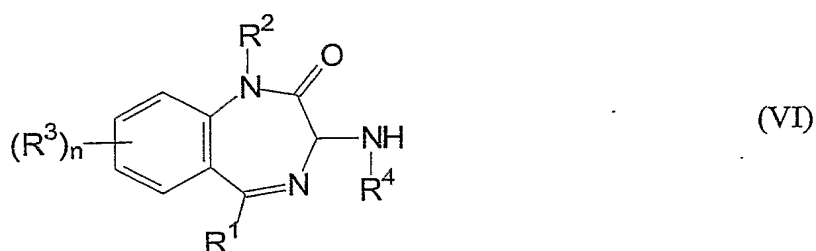
which need not be characterized.

The compound of formula (IV) can then be subjected to ammonolysis followed by ring closure in acetic acid containing ammonium acetate to obtain the protected benzodiazepine of formula (V)

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The compound of formula (V) can then be deprotected using hydrogen bromide in acetic acid to yield the deprotected amine of formula (VI).



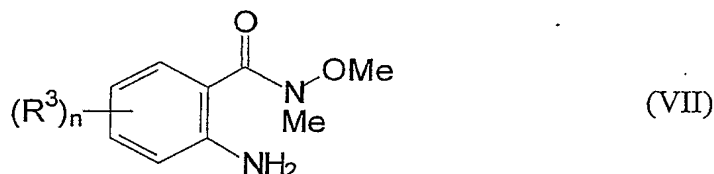
- 5 Compounds of formula (I), in which X is -CO- or -CO-NR' can be prepared by reacting a compound of formula (VI), as defined above, with an acid anhydride in a suitable solvent, preferably pyridine at ambient temperature, or with an acid chloride in a suitable solvent in the presence of a base, preferably in THF at ambient temperature with triethylamine present. Alternatively, the compounds can be
- 10 produced by reaction of a compound of formula (VI) with an acid in a suitable solvent in the presence of a base and a coupling agent, preferably in THF at ambient temperature with triethylamine and *O*-benzotriazol-1-yl-N, N, N', N'-tetramethyluronium hexafluorophosphate (HBTU) present.

- 15 If the acid chloride used is an amino carbonyl chloride, the compound of formula (I) is a urea. In the case where R' in the X moiety is hydrogen, such compounds may also be prepared by the reaction of a compound of formula (VI) with an isocyanate. This reaction is preferably carried out in THF at ambient temperature. Alternatively, the isocyanate may be prepared *in situ* from the relevant amine and phosgene, in the presence of a base, usually triethylamine, again in THF.
- 20 Compounds in which R' is other than hydrogen can, of course, be prepared by reacting a corresponding compound in which R' is hydrogen with an appropriate

alkylating agent, for example L-(C₁-C₆ alkyl) wherein L is a leaving group, for example chlorine.

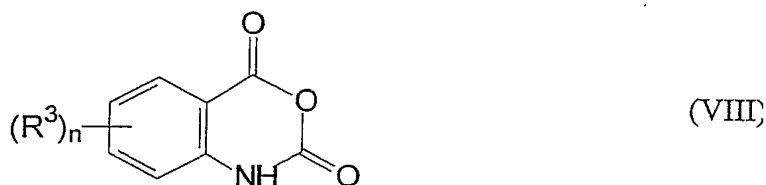
Compounds of formula (I), in which X is -S(O)₂- may be prepared by the reaction of a compound of formula (VI) with a suitable sulfonyl chloride. Similarly, compounds of formula (I), in which X is -S(O)- may be prepared by the reaction of a compound of formula (VI) with a suitable sulfinyl chloride

In the preparation of the benzodiazepine skeleton, commercially available aminobenzophenone compounds of formula (III) can be used where possible. Compounds of formula (III) which are not commercially available can be prepared by known methods, for example by reaction of a Weinreb type amide of formula (VII)



with a group R¹-Li or a Grignard reagent such as R¹-MgBr. Preferably this reaction is carried out in THF at -100°C.

Compounds of formula (VII) are known compounds or can be prepared by analogy with known methods. For example, they can be prepared from the reaction of isatoic anhydrides of formula (VIII)



with N,O-dimethyl hydroxylamine under standard reaction conditions.

The starting materials of formula (II), (III), (VII), and (VIII) are known compounds, or may be prepared by analogy with known methods.

Further synthetic manipulation of the thus obtained compounds of formula (I) may be carried out by conventional methods to achieve further compounds of

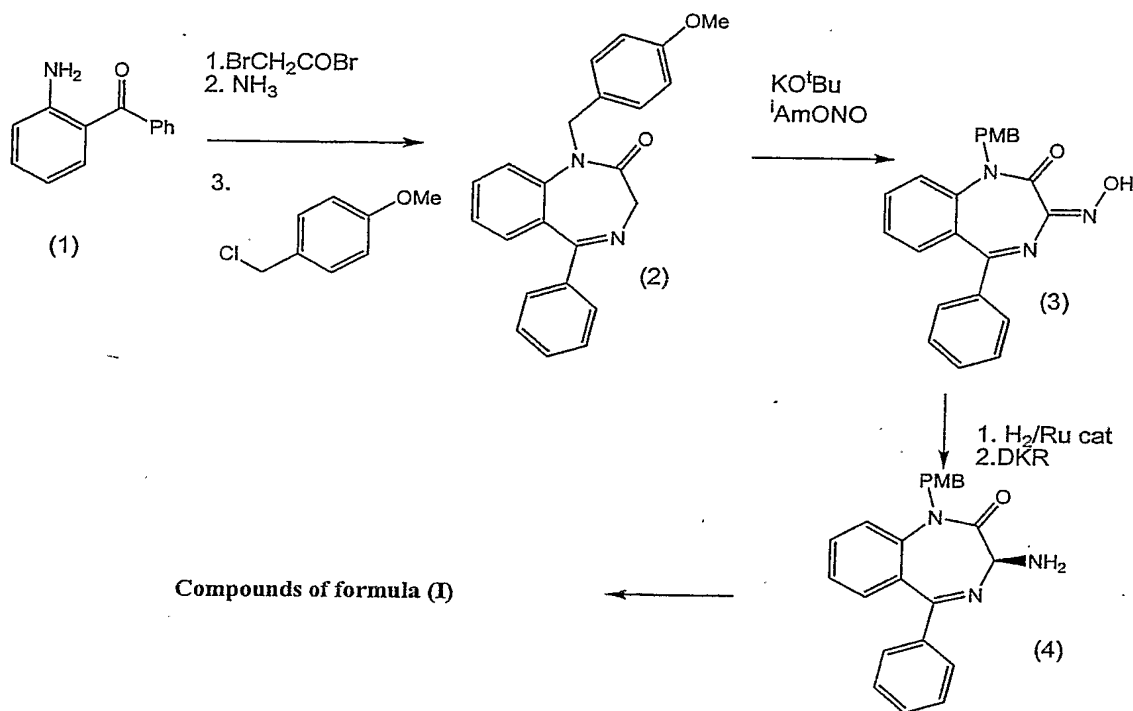
formula (I). The benzodiazepines of formula (I) can be salified by treatment with an appropriate acid or base.

Although the described route to the claimed compounds provides an adequate synthesis for laboratory scale preparations, an alternative route was sought which has potential as a manufacturing route. The same starting material (2-amino-benzophenone) (1) is used in both, however in the alternative route, the benzodiazepine ring system is formed by reaction initially with bromoacetyl bromide (or an equivalent reagent) followed by ring closure with ammonia. These reactions are carried out in a suitable solvent, such as dichloromethane, and at a suitable temperature which may range from -20 to 150°C. In order to protect the NH functionality, at this stage the unsubstituted benzodiazepine is reacted with a base, and an alkylating agent. For instance sodium hydride in DMF followed by addition of 4-methoxy-benzyl chloride gives rise to the intermediate (2) shown below. Further reaction of this material with a base (e.g. potassium tert-butoxide) in a suitable solvent (e.g. THF or DMF) followed by quenching with isoamyl nitrite (or an alternative similar reagent) furnishes the oxime intermediate (3) which may be converted into the racemic primary amine by methods which include the use of hydrogen and a suitable catalyst. This amine then undergoes a Dynamic Kinetic Resolution (DKR) procedure by which the racemic amine in the presence of a suitable optically active acid, and a suitable aldehyde gives rise to precipitation of the salt of the desired (S)-amine (4) in good yield and exceptionally high enantiomeric excess. A suitable acid for this conversion can be e.g. Camphorsulfonic acid, Boc-phenyl alanine or the like, and a suitable aldehyde may be a benzaldehyde such as 3,5-dichloro salicylaldehyde.

The optically amine thus formed may then be transformed into a desired derivative, such as an amide or urea. The amide formations may be carried out using a suitable carboxylic acid and a coupling reagent, or a carbonyl chloride or other suitable reagent, and the ureas prepared using either a suitable isocyanate, or alternatively reaction with phosgene followed by a suitable amine.

These derivatives thus formed may then have the protecting group removed. This may be carried out in the presence of a Lewis Acid, such as aluminium chloride, boron trifluoride, titanium tetrachloride, or the like. These reactions are carried out

in a suitable inert solvent, such as dichloromethane. Reaction temperatures may range from -20 to 150°C, but are typically carried out at room temperature or below.



5

As explained above, the compounds of the invention are active against RSV. The present invention therefore provides a method for treating a patient suffering from or susceptible to an RSV infection, which method comprises administering to said patient an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

RSV is prevalent among children younger than two years of age, adults suffering from asthma, chronic obstructive pulmonary disorder (COPD) or immunodeficiency and the elderly. It is a particularly serious risk amongst children who suffer from chronic lung disease. Accordingly, the said composition or medicament is typically for use in treating a patient who is a child under two years of age, patients with asthma, COPD or immunodeficiency the elderly or persons in long term care facilities. Typically, said child suffers from chronic lung disease.

Further, anti-RSV prophylaxis is recommended for infants born at 32 weeks of gestation or earlier, until they reach 6 months of age, the elderly, persons with

immunodeficiency and those in long term care facilities. Accordingly, the said composition or medicament is typically for use in preventing RSV infection in an infant less than 6 years of age, who was born after 32 weeks of gestation or less, the elderly, persons with immunosufficiency and those in long term care facilities.

5 It has been shown that RSV infections are accompanied by inflammatory reactions (Noah et al, Clinical Immunology 2000, Vol 97, 43-49). The present invention also relates to a combination of a compound of formula (I), or a pharmaceutically acceptable salt thereof, with an anti-inflammatory compound and the use of such a combination in the treatment of RSV. Typically, said anti-
10 inflammatory compound is a steroid, for example budesonide or fluticasone, a non-steroid, for example a leukotriene antagonist, phosphodiesterase 4 inhibitor or TNF alpha inhibitor or an interleukin 8 or interleukin 9 inhibitor.

Thus, in one embodiment, a compound of formula (I), or pharmaceutically acceptable salt thereof, is combined with a steroid antiinflammatory compound, for
15 example budesonide or fluticasone. In a preferred embodiment, the steroid is administered in low doses to minimize immuno-suppressant effects. In another embodiment a compound of formula (I), or a pharmaceutically acceptable salt thereof, is combined with a non-steroid anti-inflammatory compound, for example leukotriene antagonists such as Singulair (Merck) or Accolate (Astra Zeneca),
20 phosphodiesterase 4 inhibitors such as roflumilast (Altana), TNF alpha inhibitors such as Enbrel (Amgen), Remicade (Centocor), Humira (Abbott) or CDP870 (Celltech) or NSAIDS. In a further embodiment, a compound of formula (I) is combined with interleukin 8 or interleukin 9 inhibitors. The present invention thus also relates to a product containing a compound of formula (I), or a pharmaceutically
25 acceptable salt thereof, and an anti-inflammatory compound for simultaneous, separate or sequential use in the treatment of RSV.

The present invention also relates to a combination of a compound of formula (I), or a pharmaceutically acceptable salt thereof, with an anti-influenza compound and the use of such a combination in the treatment of concomitant RSV and
30 influenza infections. The present invention thus also relates to a product containing a compound of formula (I), or a pharmaceutically acceptable salt thereof, and an anti-influenza compound for simultaneous, separate or sequential use in the treatment of

concomitant RSV and influenza infections.

It is a further surprising finding of the present invention that compounds of the invention are active against human metapneumovirus, measles, parainfluenza viruses, paramyxoviruses and mumps. The present invention thus provides the use
5 of a compound of formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of human metapneumovirus, measles, parainfluenza viruses, paramyxoviruses and mumps.

The compounds of the invention may be administered in a variety of dosage forms. Thus, they can be administered orally, for example as tablets, troches,
10 lozenges, aqueous or oily suspensions, dispersible powders or granules. The compounds of the invention may also be administered parenterally, whether subcutaneously, intravenously, intramuscularly, intrasternally, transdermally or by infusion techniques. The compounds may also be administered as suppositories.

In a preferred embodiment, the compounds of the invention are administered
15 by intranasal or intrabronchial administration. The present invention also provides an inhaler or nebuliser containing a medicament which comprises (a) a benzodiazepine derivative of the formula (I), as defined above, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable carrier or diluent.

The present invention also provides a pharmaceutical composition
20 containing such a benzodiazepine derivative, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

Said pharmaceutical composition typically contains up to 85 wt% of a compound of the invention. More typically, it contains up to 50 wt% of a compound of the invention. Preferred pharmaceutical compositions are sterile and pyrogen free.
25 Further, the pharmaceutical compositions provided by the invention typically contain a compound of the invention which is a substantially pure optical isomer.

The compounds of the invention are typically formulated for administration with a pharmaceutically acceptable carrier or diluent. For example, solid oral forms may contain, together with the active compound, diluents, e.g. lactose, dextrose,
30 saccharose, cellulose, corn starch or potato starch; lubricants, e.g. silica, talc, stearic acid, magnesium or calcium stearate, and/or polyethylene glycols; binding agents; e.g. starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or

polyvinyl pyrrolidone; disaggregating agents, e.g. starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuffs; sweeteners; wetting agents, such as lecithin, polysorbates, laurylsulphates; and, in general, non toxic and pharmacologically inactive substances used in pharmaceutical formulations. Such pharmaceutical preparations may be manufactured in known manner, for example, by means of mixing, granulating, tableting, sugar coating, or film coating processes.

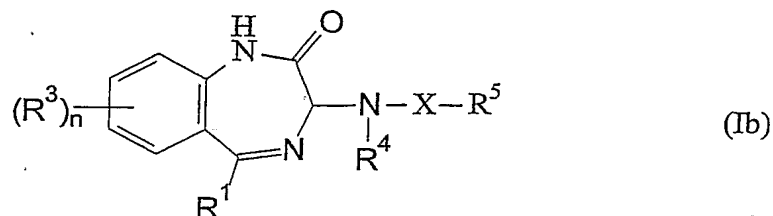
Liquid dispersions for oral administration may be syrups, emulsions and suspensions. The syrups may contain as carriers, for example, saccharose or saccharose with glycerine and/or mannitol and/or sorbitol.

Suspensions and emulsions may contain as carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, carboxymethylcellulose, or polyvinyl alcohol. The suspension or solutions for intramuscular injections may contain, together with the active compound, a pharmaceutically acceptable carrier, e.g. sterile water, olive oil, ethyl oleate, glycols, e.g. propylene glycol, and if desired, a suitable amount of lidocaine hydrochloride.

Solutions for injection or infusion may contain as carrier, for example, sterile water or preferably they may be in the form of sterile, aqueous, isotonic saline solutions.

A therapeutically effective amount of a compound of the invention is administered to a patient. A typical dose is from about 0.001 to 50 mg per kg of body weight, according to the activity of the specific compound, the age, weight and conditions of the subject to be treated, the type and severity of the disease and the frequency and route of administration. Preferably, daily dosage levels are from 5 mg to 2 g.

Certain benzodiazepine derivatives of the formula (I) are novel *per se*. The present invention includes these novel compounds and pharmaceutically acceptable salts thereof. The present invention therefore also provides compounds of formula (Ib), or a pharmaceutically acceptable salt thereof



wherein R_1 , R_3 , n , R_4 , X and R_5 are as defined above.

Typically, in the formula (Ib), R_1 is an unsubstituted phenyl group.

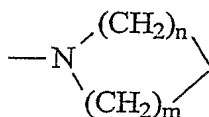
5 Typically, in the formula (Ib), when A_1 is a heteroaryl group, it is other than a 5-methyl-isoxazolyl moiety.

Typically, in the formula (Ib), A_1 is an aryl or heteroaryl moiety.

Typically, in the formula (Ib), X is $-\text{CO}-$ or $-\text{CO}-\text{NR}'-$, wherein R' is as defined above, provided that when X is $-\text{CO}-\text{NR}'-$, the moiety $-\text{A}_1-\text{Y}-\text{A}_2$ is -phenyl-
10 O-phenyl.

Typically, in the formula (Ib), A_2 is other than a 4- to 10- membered saturated cycloalkyl ring, in which one of the carbon atoms is replaced by a N atom. In particular, A_2 is typically other than a substituted or unsubstituted moiety of the formula

15



wherein n and m are the same or different and each represent an integer of from 1 to 4.

20 Typically, in the formula (Ib), A_2 is a piperazinyl, pyridyl, pyrrolidinyl, pyrazinyl, cyclopropyl, phenyl or S,S-dioxo-thiomorpholino group which is unsubstituted or is substituted by a C_1 - C_2 alkyl group.

The present invention also relates to the novel compounds, as defined above, or a pharmaceutically acceptable salt thereof, for use in a method of treating the
25 human or animal body. The present invention also relates to a pharmaceutical composition comprising a novel compound as defined above and a pharmaceutically acceptable diluant or carrier. Preferably, the pharmaceutical composition comprises

a pharmaceutically acceptable salt of a novel compound as defined above. A pharmaceutically acceptable salt is as defined above. The novel compounds of the invention are typically administered in the manner defined above and the compounds are typically formulated for administration in the manner defined above.

5 Preferably, the pharmaceutical compositions comprise optically active isomers of the novel compounds of the invention. Thus, for example, preferred novel compounds of the invention containing only one chiral centre include an R enantiomer in substantially pure form, an S enantiomer in substantially pure form and enantiomeric mixtures which contain an excess of the R enantiomer or an excess
10 of the S enantiomer. It is particularly preferred that pharmaceutical contains a compound of the invention which is a substantially pure optical isomer. For the avoidance of doubt, the novel compounds of the invention can, if desired, be used in the form of solvates.

 The following Examples illustrate the invention. They do not however, limit
15 the invention in any way. In this regard, it is important to understand that the particular assays used in the Examples section are designed only to provide an indication of anti-RSV activity. There are many assays available to determine the activity of given compounds against RSV, and a negative result in any one particular assay is therefore not determinative.

20

EXAMPLES

Intermediate 1

5 2-Chloro-4-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-benzoic acid

A mixture of 4-amino-2-chlorobenzoic acid (172mg) and ethenesulfonyl-ethene (0.15ml) in water (3ml) containing sodium carbonate (212mg) was heated to 100C for 18h. The mixture was allowed to cool and was acidified with 2N HCl. The off-
10 white precipitate was collected and dried (263mg)

LC/MS RT= 4.09mins, ES- 288,290

Intermediate 2

15

2-Chloro-5-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-benzoic acid

A mixture of 5-amino-2-chlorobenzoic acid (172mg) and ethenesulfonyl-ethene (0.15ml) in water (3ml) was heated to 100C for 18h. The mixture was allowed to
20 cool and was extracted with dichloromethane. The dried extracts were evaporated giving a pale brown solid (265mg)

LC/MS RT= 4.13mins, ES- 288,290

25 Intermediate 3

2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-nicotinic acid

This material was prepared as described for Intermediate 1 except that 2-amino-
30 nicotinic acid (138mg) was used. The title compound was isolated as an off-white solid (93mg)

Intermediate 4

2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-3-methyl-benzoic acid

- 5 This material was prepared as described for Intermediate 2 except that 2-amino-3-methyl-benzoic acid (302mg) was used. The title compound was isolated as a pale brown solid (486mg)

Intermediate 5

10

2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-4-methyl-benzoic acid

- This material was prepared as described for Intermediate 2 except that 2-amino-4-methyl-benzoic acid (302mg) was used. The title compound was isolated as a brown solid (430mg)
- 15

Intermediate 6

2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-6-methyl-benzoic acid

20

- This material was prepared as described for Intermediate 2 except that 2-amino-6-methyl-benzoic acid (302mg) was used. The title compound was isolated as a brown solid (490mg)

- 25 Intermediate 7

3-(4-Methyl-piperazine-1-sulfonyl)-benzoic acid

- A solution of 3-chlorosulfonyl-benzoic acid (89mg) 4-dimethylamino-pyridine (catalytic amount) and N-methylpiperazine (0.045ml) in dichloromethane (10ml) was heated to reflux for 2h. The solvent was then evaporated and the crude material used without purification or characterisation in the next synthetic step.
- 30

Intermediate 8

3-Piperidine-1-sulfonyl-benzoic acid

5

This material was prepared as described for Intermediate 7 except that piperidine was used as the nucleophile. As for Intermediate 7 the material was used crude.

Intermediate 9

10

3-(Morpholine-4-sulfonyl)-benzoic acid

This material was prepared as described for Intermediate 7 except that morpholine was used as the nucleophile. As for Intermediate 7 the material was used crude.

15

Intermediate 10

2-Chloro-6-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-benzoic acid

20 This material was prepared as described for Intermediate 2 except that 2-amino-6-chloro-benzoic acid (343mg) was used. The title compound was isolated as a buff solid (405mg)

Intermediate 11

25

5-Chloro-2-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-benzoic acid

This material was prepared as described for Intermediate 2 except that 2-amino-5-chloro-benzoic acid (200mg) was used. The title compound was isolated as a white solid (233mg)

30

¹H NMR (DMSO, □) 3.25 (brs, 4H) 3.47 (brs, 4H) 7.31 (d, 1H) 7.54 (dd, 1H) 7.71 (d, 1H)

LC/MS RT = 4.66 min Found $ES^+ = 290,292$

Intermediate 12

5 2-(1,1-Dioxo-1 λ 6-thiomorpholin-4-yl)-5-fluoro-benzoic acid

This material was prepared as described for Intermediate 2 except that 2-amino-5-fluoro-benzoic acid (200mg) was used. The title compound was isolated as a white solid (310mg)

10 1H NMR (DMSO, \square) 3.28 (m, 4H) 3.42 (m, 4H) 7.33-7.56 (m, 3H)

LC/MS RT = 4.28 min Found $ES^- = 272$

Intermediate 13

15 4-Fluoro-2-thiomorpholin-4-yl-benzoic acid

A mixture of 2,4-difluoro-benzoic acid (0.5g), thiomorpholine (0.33ml) and triethylamine (0.88ml) in acetonitrile (2ml) was heated to 200C in a microwave reactor for 20mins. The residue was partitioned between water and dichloromethane.

20 The dried organic layer was evaporated and then purified on a silica gel SPE cartridge. Elution with dichloromethane followed by a gradient of dichloromethane:ethanol:0.880 ammonia; 800:8:1 to 200:8:1 gave the title material as a white solid (292mg)

25 1H NMR (DMSO, \square) 2.81 (m, 4H) 3.27 (m, 4H) 7.11 (m, 1H) 7.40 (dd, 1H) 7.95 (m, 1H)

Intermediate 14

30 2-(1,1-Dioxo-4-oxy-1 λ 6-thiomorpholin-4-yl)-4-fluoro-benzoic acid

Intermediate 11 (262mg) and potassium peroxymonosulfate (1.34g) in methanol

(5ml) and water (2.5ml) was stirred at room temperature for 6h. The precipitate formed was collected by filtration then dissolved in aqueous sodium bicarbonate. Acidification to pH3 with 1M HCl led to the formation of a white precipitate which was collected and dried (194mg)

5

¹H NMR (DMSO, □) 3.2-3.48 (brn, 4H) 3.59 (t, 2H) 3.89 (t, 2H) 6.96 (m, 1H) 7.30 (dd, 1H) 7.85 (m, 1H)

Intermediate 15

10

6-Chloro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-nicotinamide

A mixture of racemic 3-amino-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one (1g), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (1.51g), triethylamine (0.83ml) and 6-chloro-nicotinic acid (0.63g) in dry DMF (20ml) was stirred at room temperature for 1.5h. Water (200ml) was then added and the mixture stirred vigorously for 10mins. The colourless precipitate was collected by filtration and dried (1.1g)

20

¹H NMR (DMSO, □) 5.50 (d, 1H) 7.28-7.71 (m, 10H) 8.42 (dd, 1H) 9.01 (d, 1H) 9.99 (d, 1H) 10.95 (s, 1H)

LC/MS RT= 4.96mins, ES+ 391,393

25

Intermediate 16

Thiomorpholine-1,1-dioxide

9.98 g of thiomorpholine and 14.8 g of triflic anhydride were stirred together in DCM at room temperature for 2 hours. The reaction was then partitioned between 1 M K₂CO_{3(aq)} and DCM. The organic layer was separated and dried by passing

through a hydrophobic frit, then concentrated *in vacuo*. 13.82 g of the resultant oil was stirred with 85.2 g of oxone in 50 mL of methanol and 50 mL of water for 18 h at room temperature. The reaction was then filtered and washed with methanol and the filtrate concentrated. This was then partitioned between water and EtOAc and the aqueous layer washed 3 times with EtOAc. The combined organic extracts were then dried (MgSO₄) and concentrated to produce a white solid. This was then stirred at room temperature with 40 g of K₂CO₃ in 80 mL of methanol for 18 h. The methanol was then removed *in vacuo* and the remains partitioned between DCM and sat. K₂CO_{3(aq)}. The combined organic extracts were passed through a hydrophobic frit and concentrated *in vacuo* to produce the title compound, 3.51 g.

¹H NMR (CDCl₃, □) 1.54 (s, 1H), 2.93-2.97 (m, 4H), 3.24-3.28 (m, 4H).

Intermediate 17

5-([(2-Methanesulfonyl-ethyl)-methyl-amino]-methyl)-furan-2-carboxylic acid ethyl ester

0.5 g of 5-chloromethyl-furan-2-carboxylic acid ethyl ester and 20 ml of 2 M methylamine solution in THF were stirred at room temperature for 5 days under nitrogen. The solution was then concentrated and purified by SPE. The resultant oil was heated at 200 °C in a microwave with 0.2mL of methanesulfonyl-ethene in 3 mL of acetonitrile for 1 h. The solution was concentrated and purified by chromatography to produce the title compound as a colourless oil.

LC/MS RT = 3.55 min, Found ES⁺ = 290

¹H NMR (CDCl₃, □) 1.29 (t, 3H), 2.25 (s, 3H), 2.92-2.88 (m, 2H), 2.99 (s, 3H), 3.06-2.99 (t, 2H), 3.6 (s, 2H), 4.26 (q, 2H), 6.28 (d, 1H), 7.04 (d, 1H).

Intermediate 18

5-Dimethylaminomethyl-furan-2-carboxylic acid

0.16ml of a 2 M solution of dimethylamine was added to a stirred suspension of 19.2 mg of sodium hydride in 2 mL of DMF under a nitrogen atmosphere at room temperature for 30 min. Then a solution of 5-chloromethyl-furan-2-carboxylic acid ethyl ester in 2 mL of DMF was added dropwise over a period of 30 min. The reaction was then allowed to stir for 2 days. The solvent was then removed *in vacuo* and 5 mL of EtOH and 0.35ml of 2 M NaOH added and stirred at 80 °C for 40 min. Upon return the reaction was acidified below pH 5.0 and the solvent removed *in vacuo* to produce the title compound to be hydrolysed and then used crude in the next stage

Intermediates 19-23 were prepared in an analogous manner and were used without characterisation in the next synthetic step

15. Intermediate 19

5-Morpholin-4-ylmethyl-furan-2-carboxylic acid

Intermediate 20

20

5-(1,1-Dioxo-1 λ 6-thiomorpholin-4-ylmethyl)-furan-2-carboxylic acid

Intermediate 21

25 5-(4-Methyl-piperazin-1-ylmethyl)-furan-2-carboxylic acid

Intermediate 22

5-(Piperidin-1-ylmethyl)-furan-2-carboxylic acid

30

Intermediate 23

5-(Pyrrolidin-1-ylmethyl)-furan-2-carboxylic acid

Intermediate 24

5 3-Cyclopropyl-1,3-dihydro[4,5-b]pyridin-2-one

A mixture of 2-chloro-3-nitro-pyridine (2g), cyclopropylamine (1.13ml) and potassium carbonate (3.48g) in acetonitrile (30ml) was stirred at room temperature for 18h. The mixture was then partitioned between water and ethyl acetate. The dried
10 extracts were evaporated giving a bright yellow solid (2.1g)

This material was then hydrogenated at atmospheric pressure in ethanol (150ml) over palladium on carbon catalyst (10%, 100mg). When hydrogen uptake had ceased the mixture was filtered through celite and evaporated giving a dark gum (1.7g)

This material was then dissolved in dry THF (40ml) and was treated with carbonyl
15 di-imidazole (2.2g) at reflux for 2.5h. The mixture was then partitioned between water and ethyl acetate. The dried organic extract was evaporated leaving a dark gum, which was crystallised from ethyl acetate/petrol giving a colourless solid (1.2g)

¹H NMR (DMSO, \square) 0.97-1.04 (m, 4H) 2.92 (m, 1H) 6.97 (dd, 1H) 7.22 (dd, 1H)
20 7.92 (dd, 1H) 10.95 (brs, 1H)

Intermediate 25

2-Morpholin-4-ylmethyl-furan-3-carboxylic acid methyl ester

25

A mixture of 2-chloromethyl-furan-3-carboxylic acid methyl ester (100mg) and morpholine (0.08ml) in acetonitrile (4ml) was stirred at room temperature for 2h. The mixture was then partitioned between dichloromethane and aqueous sodium bicarbonate solution. The dried organic layer was evaporated giving a yellow oil

30 (75mg)

¹H NMR (CDCl₃, \square) 2.57 (m, 4H) 3.74 (m, 4H) 3.86 (s, 3H) 3.97 (s, 2H) 6.70 (d,

1H) 7.38 (d, 1H)

Intermediate 26

5 3-Morpholin-4-ylmethyl-benzoic acid methyl ester

This material was prepared as for Intermediate 25. The product was a colourless oil (210mg)

10 ¹H NMR (CDCl₃, □) 2.43 (m, 4H) 3.53 (s, 2H) 3.70 (m, 4H) 3.91 (s, 3H) 7.39 (t, 1H) 7.42 (dd, 1H) 7.93 (dt, 1H) 7.99 (brs, 1H)

Intermediate 27

15 5-Morpholin-4-ylmethyl-isoxazole-3-carboxylic acid methyl ester

5-Methyl-isoxazole-3-carboxylic acid methyl ester (200mg), N-bromosuccinimide (252mg) and benzoyl peroxide (30mg) in dry chloroform (4ml) was stirred and heated to 85C for 5h. The solution was cooled to room temperature and was treated with morpholine (0.27ml). Stirring was continued for 20h and the mixture was then partitioned between water and dichloromethane. The dried organic extract was evaporated and the residue purified on a silica gel SPE cartridge. Elution with dichloromethane followed by dichloromethane:ethanol:0.880 ammonia; 200:8:1 gave a colourless oil (50mg)

25 ¹H NMR (CDCl₃, □) 2.46 (m, 4H) 3.64 (m, 4H) 3.67 (s, 2H) 3.90 (s, 3H) 6.55 (s, 1H)

Intermediates 28-30 were prepared in an analogous method to Intermediate 25

30

Intermediate 28

3-Morpholin-4-ylmethyl-furan-2-carboxylic acid methyl ester

This compound was isolated as a yellow oil (189mg)

5 ^1H NMR (CDCl_3 , \square) 2.45 (m, 4H) 3.65 (m, 4H) 3.71 (s, 2H) 3.85 (s, 3H) 6.56 (d, 1H) 7.45 (d, 1H)

Intermediate 29

10 3-Morpholin-4-ylmethyl-thiophene-2-carboxylic acid methyl ester

This compound was isolated as yellow oil (197mg).

15 ^1H NMR (CDCl_3 , \square) 2.50 (m, 4H) 3.69 (s, 2H) 3.72 (m, 4H) 3.86 (s, 3H) 6.90 (d, 1H) 7.64 (d, 1H)

Intermediate 30

5-Morpholin-4-ylmethyl-thiophene-2-carboxylic acid methyl ester

20

This compound was isolated as a yellow oil (214mg).

^1H NMR (CDCl_3 , \square) 2.44 (m, 4H) 3.64 (m, 4H) 3.79 (s, 3H) 3.84 (s, 2H) 7.15 (d, 1H) 7.36 (d, 1H)

25

Intermediates 25-30 were hydrolysed to the corresponding carboxylic acids before use in the final coupling step of the synthetic sequence

Intermediate 31

30

4-Fluoro-2-morpholin-4-yl-benzoic acid

2,4-Difluoro-benzoic acid (50mg) and morpholine (0.03ml) in acetonitrile (0.5ml) were heated in a microwave at 200C for 15mins. The solvent was evaporated leaving a dark gum which was used without purification in the next synthetic step.

5 Intermediate 32

4-Fluoro-2-piperidin-1-yl-benzoic acid

This was prepared in an analogous procedure to Intermediate 31.

10

Intermediates 33-5 were prepared in an analogous procedure to Intermediate 31 except that 2-fluoro-4-trifluoromethyl-benzoic acid was used.

Intermediate 33

15

2-Pyrrolidin-1-yl-4-trifluoromethyl-benzoic acid

Intermediate 34

20 2-Piperidin-1-yl-4-trifluoromethyl-benzoic acid

Intermediate 35

2-Morpholin-4-yl-4-trifluoromethyl-benzoic acid

25

Intermediates 36 and 37 were prepared in an analogous procedure to Intermediate 31 except that 2-fluoro-5-trifluoromethyl-benzoic acid was used.

Intermediate 36

30

2-Pyrrolidin-1-yl-5-trifluoromethyl-benzoic acid

Intermediate 37

2-Morpholin-4-yl-5-trifluoromethyl-benzoic acid

- 5 Intermediates 38 and 39 were prepared in an analogous procedure to Intermediate 31 except that 4-cyano-2-fluoro-benzoic acid was used.

Intermediate 38

10 4-Cyano-2-pyrrolidin-1-yl-benzoic acid

Intermediate 39

4-Cyano-2-piperidin-1-yl-benzoic acid

15

Example 1.

6-(4-Methyl-piperazin-1-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-nicotinamide

20

- Intermediate 15 (50mg) and N-methylpiperazine (0.022ml) in acetonitrile (1ml) containing triethylamine (0.027ml) was heated in a microwave at 200°C for 10mins. The mixture was then partitioned between water and dichloromethane. The dried organic layer was evaporated and the residue purified on a silica gel SPE cartridge. Gradient elution with 5-10% methanol in dichloromethane gave a colourless solid (10mg)
- 25

- 1H NMR (DMSO, d) 2.28 (s, 3H) 2.45 (m, 4H) 3.68 (m, 4H) 5.56 (d, 1H) 6.93 (d, 1H) 7.32-7.72 (m, 10H) 8.20 (dd, 1H) 8.82 (d, 1H) 9.42 (d, 1H) 10.94 (s, 1H)
- 30 RT= 3.94mins, ES+ 455

Example 2

3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

- 5 This material was prepared as for Example 1 except that piperidine was used as the nucleophile. The product was a colourless solid (15mg)

¹H NMR (DMSO, d) 1.54-1.63 (brn, 6H) 3.65 (m, 4H) 5.48 (d, 1H) 6.86 (d, 1H) 7.25-7.65 (m, 10H) 8.11 (dd, 1H) 8.75 (d, 1H) 9.32 (d, 1H)

10 RT= 4.54 mins, ES+ 440

Example 3

(S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

- (S)-3-Amino-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one (100mg), O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (150mg), 2-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-benzoic acid (102mg) and triethylamine (0.083ml) in dry DMF (1ml) was stirred at room temperature for 1h. Water (10ml) was then added and stirring continued for 10mins. The colourless precipitate was collected by filtration and then partitioned between dichloromethane and water. The dried organic phase was evaporated and the residue purified on a silica gel SPE cartridge. Elution with ethyl acetate: petrol 1:1 gave the title compound as a colourless solid (140mg)

¹H NMR (DMSO, □) 3.49 (brs, 8H) 5.48 (d, 1H) 7.31-7.95 (m, 13H) 10.86 (d, 1H) 11.18 (s, 1H)

Example 4

(S)-2-Chloro-4-morpholin-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as for Example 3 except that 2-chloro-4-morpholin-4-yl-benzoic acid (86mg) was used. The title compound was a colourless solid (112mg).

5 ¹H NMR (DMSO, □) 3.21 (m, 4H) 3.70 (t, 4H) 5.36 (d, 1H) 6.90-6.97 (m, 2H) 7.21-7.66 (m, 10H) 9.21 (d, 1H) 10.86 (s, 1H)

Example 5

10 (S)-2-(1,1-Dioxo-4-oxy-1λ6-thiomorpholin-4-yl)-4-fluoro-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as for Example 3 except that 2-(1,1-dioxo-4-oxy-1λ6-thiomorpholin-4-yl)-benzoic acid (Intermediate 14, 30mg) was used. The title
15 compound was a colourless solid (29mg).

¹H NMR (DMSO, d) 3.32-3.98 (m, 8H) 5.34 (d, 1H) 6.99 (dt, 1H) 7.16-7.65 (m, 11H) 9.51 (d, 1H) 10.98 (s, 1H)
RT= 5.09mins, ES+ 523

20

Example 6

(S)-5-Chloro-2-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

25

This material was prepared as for Example 3 except that 5-Chloro-2-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-benzoic acid (Intermediate 11, 58mg) was used. The title
compound was a colourless solid (70mg).

30 ¹H NMR (DMSO, d) 3.54 (s, 8H) 5.53 (d, 1H) 7.37-7.75 (m, 11H) 7.90 (d, 1H) 10.84 (d, 1H) 11.24 (s, 1H)
RT= 5.38mins, ES+ 523, 525

Example 7

5 (S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-5-fluoro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as for Example 3 except that 5-Fluoro-2-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-benzoic acid (Intermediate 12, 54mg) was used. The title compound was a colourless solid (70mg).

10

¹H NMR (DMSO, d) 3.49 (m, 8H) 5.47 (d, 1H) 7.34-7.69 (m, 12H) 11.12 (d, 1H) 11.20 (s, 1H)

RT = 5.19mins, ES+ 507

15 Example 8

(S)-5-(4-Methyl-piperazin-1-ylmethyl)-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

20 This material was prepared as for Example 3 except that 5-(4-Methyl-piperazin-1-ylmethyl)-furan-2-carboxylic acid (Intermediate 21) was used. The title compound was a colourless solid (15mg).

25 ¹H NMR (CDCl₃, d) 2.23 (s, 3H), 2.43-2.51 (m, 8H), 3.56 (s, 2H), 5.65 (d, 1H), 6.29 (d, 1H), 7.05-7.51 (m, 11H), 7.92 (d, 1H).

RT = 4.10 mins, ES+ 458

Example 9

30 (S)-5-Pyrrolidin-1-ylmethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as for Example 3 except that 5-(pyrrolidin-1-ylmethyl)-furan-2-carboxylic acid (Intermediate 23) was used. The title compound was a colourless solid (52mg).

5 ¹H NMR (CDCl₃, d) 1.76-1.77 (m, 4H), 2.60-2.62 (m, 4H), 3.71 (s, 2H), 5.64 (d, 1H), 6.31 (d, 1H), 7.05-7.50 (m, 10H), 7.98 (d, 1H), 8.04 (s, 1H).
RT = 4.09 mins, ES+ 403

Example 10

10

(S)-5-Piperidin-1-ylmethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as for Example 3 except that 5-(piperidin-1-ylmethyl)-furan-2-carboxylic acid (Intermediate 22) was used. The title compound was a colourless solid (21mg).

15 ¹H NMR (CDCl₃, d) 1.36-1.45 (m, 2H), 1.53-1.60 (m, 4H), 2.45-2.55 (m, 4H), 3.62 (s, 2H), 5.65 (d, 1H), 6.34 (d, 1H), 7.06-5.52 (m, 10H), 7.81-7.89 (m, 1H), 7.96 (d, 20 1H).
RT = 4.16 mins, ES+ 443

Example 11

25 (S)-5-Dimethylaminomethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as for Example 3 except that 5-dimethylaminomethyl-furan-2-carboxylic acid (Intermediate 18) was used. The title compound was a colourless solid (5mg).

30 ¹H NMR (DMSO, d) 2.35 (s, 6H), 3.69 (s, 2H), 5.56 (d, 1H), 6.65 (d, 1H), 7.48-7.85

(m, 10H), 9.1 (d, 1H), 11.13 (s, 1H).

RT = 4.09 mins, ES+ 403

Example 12

5

(S)-4-Fluoro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-piperidin-1-yl-benzamide

10 This material was prepared as for Example 3 except that 4-fluoro-2-piperidin-1-yl-benzoic acid (Intermediate 32) was used. The title compound was a colourless solid (58mg).

¹H NMR (DMSO, d) 1.62-1.67 (m, 2H) 1.91-1.99 (m, 4H) 3.08-3.16 (m, 4H) 5.56 (d, 1H) 7.15-7.79 (m, 11H) 8.10-8.13 (m, 1H) 11.08 (s and d, 2H)

15 RT= 6.02mins, ES+ 457

Example 13

20 (S)-4-Fluoro-2-morpholino-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as for Example 3 except that 4-fluoro-2-morpholin-4-yl-benzoic acid (Intermediate 31) was used. The title compound was a colourless solid (19mg).

25

¹H NMR (DMSO, d) 2.94-3.00 (m, 4H) 3.71-3.82 (m, 4H) 5.35 (d, 1H) 6.98-7.85 (m, 12H) 10.52 (d, 1H) 10.90 (s, 1H)

RT= 5.34mins, ES+ 459

30 Example 14

(S)-4-Cyano-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-

pyrrolidin-1-yl-benzamide

This material was prepared as for Example 3 except that 4-cyano-2-pyrrolidin-1-yl-benzoic acid (Intermediate 38) was used. The title compound was a colourless solid
5 (13mg).

¹H NMR (DMSO, d) 1.87 (brs, 4H) 3.29 (brs, 4H) 5.37(d, 1H) 7.01-7.65 (m, 12H)
9.60 (d, 1H) 10.88 (s, 1H)

RT= 5.45mins, ES+ 450

10

Example 15

(S)-4-Cyano-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-piperidine-1-yl-benzamide

15

This material was prepared as for Example 3 except that 4-cyano-2-piperidin-1-yl-benzoic acid (Intermediate 39) was used. The title compound was a colourless solid
(27mg).

20 ¹H NMR (DMSO, d) 1.32-1.36 (m, 2H) 1.58-1.67 (m, 4H) 2.81-2.89 (m, 4H) 5.25
(d, 1H) 7.10-7.83 (m, 12H) 10.70 (d, 1H) 10.81 (s, 1H)

RT= 5.88mins, ES+ 464

Example 16

25

(S)-N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-pyrrolidin-1-yl-4-trifluoromethyl-benzamide

This material was prepared as for Example 3 except that 2-pyrrolidin-1-yl-4-trifluoromethyl-benzoic acid (Intermediate 33) was used. The title compound was a
30 colourless solid (5mg).

¹H NMR (DMSO, d) 1.89-1.92 (brs, 4H) 3.29-3.32 (brs, 4H) 5.40 (d, 1H) 6.88 (s, 1H) 6.94 (d, 1H) 7.24-7.67 (m, 10H) 9.56 (d, 1H) 10.89 (s, 1H)
RT= 5.91mins, ES+ 493

5 Example 17

(S)-N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-piperidin-1-yl-4-trifluoromethyl-benzamide

- 10 This material was prepared as for Example 3 except that 2-piperidin-1-yl-4-trifluoromethyl-benzoic acid (Intermediate 34) was used. The title compound was a colourless solid (14mg).

¹H NMR (DMSO, d) 1.53-1.57 (m, 2H) 1.80-1.91 (m, 4H) 3.00-3.14 (m, 4H) 5.46 (d, 1H) 7.30-7.72 (m, 11H) 8.09 (d, 1H) 10.98 (d, 1H) 10.99 (s, 1H)
15 RT=6.39mins, ES+ 507

Example 18

- 20 (S)-2-Morpholin-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-4-trifluoromethyl-benzamide

This material was prepared as for Example 3 except that 2-morpholin-4-yl-4-trifluoromethyl-benzoic acid (Intermediate 35) was used. The title compound was a
25 colourless solid (14mg).

¹H NMR (DMSO, d) 3.18-3.24 (m, 4H) 3.90-3.96 (m, 4H) 5.52 (d, 1H) 7.36-8.10 (m, 12H) 10.59 (d, 1H) 11.10 (s, 1H)
RT= 5.72mins, ES+ 509

30

Example 19

(S)-N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-pyrrolidin-1-yl-5-trifluoromethyl-benzamide

5 This material was prepared as for Example 3 except that 2-pyrrolidin-1-yl-5-trifluoromethyl-benzoic acid (Intermediate 36) was used. The title compound was a colourless solid (8mg).

¹H NMR (DMSO, d) 2.00-2.02 (brs, 4H) 3.40-3.43 (brs, 4H) 5.48 (d, 1H) 6.90 (d, 1H) 7.34-7.74 (m, 11H) 9.71 (d, 1H) 10.98 (s, 1H)

10 RT= 5.84 mins, ES+ 493

Example 20

15 (S)-2-Morpholin-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-trifluoromethyl-benzamide

This material was prepared as for Example 3 except that 2-morpholin-4-yl-5-trifluoromethyl-benzoic acid (Intermediate 37) was used. The title compound was a colourless solid (19mg).

20

¹H NMR (DMSO, d) 3.13-3.18 (m, 4H) 3.85-3.90 (m, 4H) 5.46 (d, 1H) 7.30-7.69 (m, 10H) 7.88 (dd, 1H) 8.04 (d, 1H) 10.37 (d, 1H) 11.04 (s, 1H)

RT= 5.72mins, ES+ 509

25 Example 21

(S)-2-Morpholin-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-nicotinamide

30 This material was prepared as for Example 3 except that 2-morpholin-4-yl-nicotinic acid was used. The title compound was a colourless solid (45mg).

¹H NMR (DMSO, d) 3.30-3.36 (m, 4H) 3.82-3.85 (m, 4H) 5.45 (d, 1H) 7.14-7.17 (m, 1H) 7.19-7.71 (m, 9H) 8.07 (dd, 1H) 8.44 (dd, 1H) 10.00 (d, 1H) 11.05 (s, 1H)
RT= 4.86mins, ES+ 442

5 Example 22

(S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-nicotinamide

- 10 This material was prepared as for Example 3 except that 2-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-nicotinic acid (Intermediate 3) was used. The title compound was a colourless solid (10mg).

¹H NMR (DMSO, d) 3.25 (t, 2H) 3.40 (t, 2H) 3.75-3.88 (m, 4H) 5.47 (d, 1H) 6.67-6.72 (m, 1H) 7.28-7.67 (m, 8H) 8.24- 8.38 (m, 3H) 9.56 (d, 1H) 10.92 (s, 1H)
15 RT= 4.43mins, ES+ 508

Example 23

- 20 (S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-3-methyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as for Example 3 except that 2-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-3-methyl-benzoic acid (Intermediate 4) was used. The title
25 compound was a colourless solid (65mg).

¹H NMR (DMSO, d) 2.36 (s, 3H) 3.24 (brs, 4H) 3.49 (brs, 4H) 5.43 (d, 1H) 7.11-7.68 (m, 12H) 9.61 (d, 1H) 10.99 (s, 1H)
RT= 5.04mins, ES+ 503

30

Example 24

(S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-4-methyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as for Example 3 except that 2-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-4-methyl-benzoic acid (Intermediate 5) was used. The title compound was a colourless solid (72mg).

¹H NMR (DMSO, d) 2.39 (s, 3H) 3.44-3.54 (brn, 8H) 5.46 (d, 1H) 7.14 (d, 1H) 7.31-7.69 (m, 10H) 7.86 (d, 1H) 10.94 (d, 1H) 11.17 (s, 1H)

RT= 5.20mins, ES+ 503

Example 25

(S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-6-methyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as for Example 3 except that 2-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-6-methyl-benzoic acid (Intermediate 6) was used. The title compound was a colourless solid (32mg).

¹H NMR (DMSO, d) 2.27 (s, 3H) 3.24-3.27 (m, 4H) 3.41-3.43 (m, 4H) 5.56 (d, 1H) 7.03 (d, 1H) 7.11 (d, 1H) 7.25-7.68 (m, 10H) 9.44 (d, 1H) 10.96 (s, 1H)

RT=5.03mins, ES+ 503

Example 26

(S)-2-Chloro-6-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as for Example 3 except that 2-chloro-6-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-benzoic acid (Intermediate 10) was used. The title compound was a colourless solid (51mg).

¹H NMR (DMSO, d) 3.43-3.47 (m, 4H) 3.59-3.61 (m, 4H) 5.63 (d, 1H) 7.39-7.83 (m, 12H) 9.86 (d, 1H) 11.14 (s, 1H)
RT= 5.07mins, ES+ 523, 525

5

Example 27

(S)-3-Cyclopropyl-2-oxo-2,3-dihydro-imidazo[4,5-b]pyridine-1-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

10

3-Cyclopropyl-1,3-dihydro[4,5-b]pyridin-2-one (Intermediate 24, 35mg), triethylamine (0.028ml) and triphosgene (20mg) were stirred at room temperature in dichloromethane (3ml) for 1h. (S)-3-Amino-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one (50mg) was then added, and stirring continued for 18h.

15 The solvent was evaporated and the residue purified on a silica gel SPE cartridge. Elution with dichloromethane:ethanol:0.880 ammonia; 200:8:1 gave a colourless solid (3mg)

¹H NMR (DMSO, d) 0.88-1.09 (m, 4H) 2.92 (m, 1H) 5.25 (d, 1H) 7.06-7.71 (m, 20 10H) 8.08 (m, 2H) 9.94 (d, 1H) 11.08(s, 1H)
RT= 4.90mins, ES+ 453

Example 28

25 (S)-3-(4-Methyl-piperazine-1-sulfonyl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as for Example 3 except that 3-(4-methyl-piperazine-1-sulfonyl)-benzoic acid (Intermediate 7) was used. The title compound was a pale 30 yellow solid (23mg).

¹H NMR (CDCl₃, d) 2.19 (s, 3H), 2.39-2.43 (m, 4H), 2.95-3.05 (m, 4H), 5.68 (d,

1H), 6.5 (s, 1H), 7.13 (t, 2H), 7.19 (s, 1H), 7.32-7.83 (m, 8H), 8.08-8.11 (m, 2H), 8.28-8.29 (m, 1H).

RT = 4.25 mins, ES+ 518

5 Example 29

(S)-4-(4-Methyl-piperazin-1-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

- 10 This material was prepared as for Example 3 except that 4-(4-methyl-piperazine-1-yl)-benzoic acid was used. The title compound was a colourless solid (46mg).

1H NMR (CDCl₃, d) 2.30 (s, 3H), 2.50-2.54 (m, 4H), 3.26-3.30 (m, 4H), 5.70 (d, 1H), 6.86 (d, 2H), 7.14 (t, 1H), 7.17-7.50 (m, 8H), 7.74 (d, 1H), 7.80 (d, 2H), 8.25-

- 15 8.40 (m, 1H).

RT = 4.16 mins, ES+ 454

Example 30

- 20 (S)-N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-(piperidine-1-sulfonyl)-benzamide

This material was prepared as for Example 3 except that 3-piperidine-1-sulfonyl-benzoic acid (Intermediate 8) was used. The title compound was a colourless solid

- 25 (35mg).

1H NMR (CDCl₃, d) 1.35-1.38 (m, 2H), 1.57-1.65 (m, 4H), 2.91-2.99 (m, 4H), 5.70 (d, 1H), 7.14 (t, 2H), 7.19 (s, 2H), 7.31-7.84 (m, 7H), 8.04-8.12 (m, 2H), 8.28-8.29 (m, 1H), 8.41 (s, 1H).

- 30 RT = 5.47 mins, ES+ 503

Example 31

(S)-3-(Morpholine-4-sulfonyl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

- 5 This material was prepared as for Example 3 except that 3-(morpholine-4-sulfonyl)-benzoic acid (Intermediate 9) was used. The title compound was a colourless solid (29mg).

1H NMR (CDCl₃, d) 2.97-3.00 (m, 4H), 3.66-3.70 (m, 4H), 5.68 (d, 1H), 7.10-8.18 (m, 13H), 8.29-8.31 (m, 2H).
10 RT = 5.06 mins, ES+ 505

Example 32

- 15 (S)-5-Morpholin-4-ylmethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as for Example 3 except that 5-morpholin-4-ylmethyl-furan-2-carboxylic acid (Intermediate 19) was used. The title compound was a
20 colourless solid (35mg).

1H NMR (CDCl₃, d) 2.46-2.49 (m, 4H), 3.55 (s, 2H), 3.66-3.70 (m, 4H), 5.65 (d, 1H), 6.30 (d, 1H), 7.06-7.51 (m, 10H), 7.95 (d, 1H), 8.38 (s, 1H).

RT = 4.28 mins, ES+ 445

25

Example 33

(S)-5-Hydroxymethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

30

This material was prepared as for Example 3 except that the hydrolysis product of 5-chloromethyl-furan-2-carboxylic acid ethyl ester was used. The title compound was a

colourless solid (48mg).

¹H NMR (CDCl₃, d) 2.78 (s, 1H), 4.55-4.56 (m, 2H), 5.63 (d, 1H), 6.25 (d, 1H), 7.00 (d, 1H), 7.09 (t, 2H), 7.15-7.49 (m, 7H), 8.10 (d, 1H), 8.46 (s, 1H).

5 RT = 4.54 mins, ES+ 376

Example 34

10 (S)-5-(1,1-Dioxo-1λ6-thiomorpholin-4-ylmethyl)-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as for Example 3 except that 5-(1,1-Dioxo-1λ6-thiomorpholin-4-ylmethyl)-furan-2-carboxylic acid (Intermediate 20) was used. The title compound was a colourless solid (192mg).

15

¹H NMR (CDCl₃, d) 3.00-3.10 (m, 8H), 3.68 (s, 2H), 5.65 (d, 1H), 6.32 (d, 1H), 7.06-7.50 (m, 10H), 7.95 (d, 1H), 8.08-8.16 (s, 1H).

RT = 4.65 mins, ES+ 493

20 Example 35

(S)-2-Chloro-4-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

25 This material was prepared as for Example 3 except that 2-chloro-4-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-benzoic acid (Intermediate 1) was used. The title compound was a colourless solid (41mg).

30 ¹H NMR (DMSO, d) 3.15 (brs, 4H) 3.92 (brs, 4H) 5.41 (d, 1H) 7.10-7.68 (m, 12H) 9.26 (d, 1H) 10.92 (s, 1H)

RT= 4.70mins, ES+ 523, 525

Example 36

(S)-2-Chloro-5-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

5

This material was prepared as for Example 3 except that 2-chloro-5-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-benzoic acid (Intermediate 2) was used. The title compound was a colourless solid (69mg).

10 ¹H NMR (DMSO, d) 3.14 (brs, 4H) 3.81 (brs, 4H) 5.37 (d, 1H) 7.08-7.63 (m, 12H)
9.56 (d, 1H) 10.84 (s, 1H)
RT= 4.76mins, ES+ 523,525

Example 37

15

(S)-5-{[(2-Methanesulfonyl-ethyl)-methyl-amino]-methyl}-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl-amide

20 This material was prepared as for Example 3 except that 5-{[(2-methanesulfonyl-ethyl)-methyl-amino]-methyl}-furan-2-carboxylic acid ethyl ester (Intermediate 17) was used. The title compound was a colourless solid (87mg).

¹H NMR (DMSO, d) 2.05 (s, 3H), 2.61 (t, 2H), 2.84 (s, 3H), 3.12 (t, 2H), 3.48 (s, 2H), 5.21 (d, 1H), 6.34 (d, 1H), 7.05-7.39 (m, 9H), 7.50 (td, 1H), 8.77 (d, 1H), 10.78
25 (s, 1H).
RT = 4.78 mins, ES+ 495

Example 38

30 (S)-2-Pyridin-3-yl-thiazole-4-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as for Example 3 except that 2-pyridin-3-yl-thiazole-4-carboxylic acid was used. The title compound was a colourless solid (55mg).

1H NMR (DMSO, d) 5.64 (d, 1H) 7.48-7.86 (m, 10H) 8.66 (dt, 1H) 8.73 (s, 1H) 8.93 (dd, 1H) 9.31 (d, 1H) 9.47 (d, 1H) 11.28 (s, 1H)
RT=4.70mins, ES+ 440

Example 39

10 (S)-2-Pyridin-4-yl-thiazole-4-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as for Example 3 except that 2-pyridin-4-yl-thiazole-4-carboxylic acid was used. The title compound was a colourless solid (54mg).

15 1H NMR (DMSO, d) 5.36 (d, 1H) 7.19-7.58 (m, 9H) 7.96 (dd, 2H) 8.53 (s, 1H) 8.69 (dd, 2H) 9.02 (d, 1H) 11.01 (s, 1H)
RT= 4.69mins, ES+ 440

20 Example 40

(S)-4-Methyl-2-pyrazin-2-yl-thiazole-5-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

25 This material was prepared as for Example 3 except that 4-methyl-2-pyrazin-2-yl-thiazole-5-carboxylic acid was used. The title compound was a colourless solid (67mg).

30 1H NMR (DMSO, d) 2.56 (s, 3H) 5.25 (d, 1H) 7.10-7.49 (m, 9H) 8.58-8.63 (s+dd, 2H) 9.16 (d, 1H) 9.38 (d, 1H) 10.78 (s, 1H)
RT= 4.82mins, ES+ 455

Example 41

(S)-2-Morpholin-4-ylmethyl-furan-3-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

5

This material was prepared as for Example 3 except that 2-morpholin-4-ylmethyl-furan-3-carboxylic acid (Intermediate 25) was used. The title compound was a colourless solid (24mg).

10 ¹H NMR (DMSO, d) 2.58 (brm, 4H) 3.67 (brm, 4H) 3.91 (s, 2H) 5.45 (d, 1H) 6.88 (d, 1H) 7.33-7.75 (m, 10H) 10.95 (s, 1H) 11.01 (d, 1H)
RT= 5.04mins, ES+ 445

Example 42

15

(S)-3-Morpholin-4-ylmethyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

This material was prepared as for Example 3 except that 3-morpholin-4-ylmethyl-benzoic acid (Intermediate 26) was used. The title compound was a colourless solid (24mg).

20 ¹H NMR (DMSO, d) 2.39 (brm, 4H) 3.55 (s, 2H) 3.60 (brm, 4H) 5.51 (d, 1H) 7.28-7.71(m, 11H) 7.93 (s, 1H) 7.97 (s, 1H) 9.50 (d, 1H) 10.93 (s, 1H)
25 RT= 4.86mins, ES+ 455

Example 43

(S)-5-Morpholin-4-ylmethyl-isoxazole-3-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

30

This material was prepared as for Example 3 except that 5-morpholin-4-ylmethyl-

isoxazole-3-carboxylic acid (Intermediate 27) was used. The title compound was a colourless solid (11mg).

1H NMR (DMSO, d) 2.93 (m, 4H) 3.46 (m, 4H) 3.66 (brs, 2H) 5.26 (d, 1H) 6.77 (s, 1H) 7.13-7.38 (m, 9H) 9.17 (d, 1H) 10.90 (s, 1H)
RT= 4.75mins, ES+ 446

Example 44

10 (S)-3-Morpholin-4-ylmethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as for Example 3 except that 3-morpholin-4-ylmethyl-furan-2-carboxylic acid (Intermediate 28) was used. The title compound was a colourless solid (20mg).

1H NMR (DMSO, d) 2.52 (brm, 4H) 3.62 (brs, 4H) 3.67 (m, 2H) 5.39 (d, 1H) 6.67 (d, 1H) 7.25-7.71 (m, 9H) 7.84 (d, 1H) 10.93 (s, 1H) 11.34 (d, 1H)
RT= 4.96mins, ES+ 445

20

Example 45

(S)-5-Pyridin-2-yl-thiophene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

25

This material was prepared as for Example 3 except that 5-pyridin-2-yl-thiophene-2-carboxylic acid was used. The title compound was a colourless solid (32mg).

1H NMR (DMSO, d) 5.58 (d, 1H) 7.37-7.77 (m, 10H) 7.96-7.99 (m, 2H) 8.10 (d, 1H) 8.32 (d, 1H) 8.67 (d, 1H) 9.81 (d, 1H) 11.03 (s, 1H)
RT= 4.91mins, ES+ 439

30

Example 46

(S)-2-Methyl-4-(morpholin-4-sulfonyl)-furan-3-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

5

This material was prepared as for Example 3 except that 2-methyl-4-(morpholin-4-sulfonyl)-furan-3-carboxylic acid was used. The title compound was a colourless solid (75mg).

10 ¹H NMR (DMSO, d) 2.77 (s, 3H) 3.26 (m, 4H) 3.85 (m, 4H) 5.60 (d, 1H) 7.43-7.83 (m, 9H) 8.23 (s, 1H) 9.68 (d, 1H) 11.07 (s, 1H)
RT= 4.90mins, ES+ 509

Example 47

15

(S)-6-Morpholin-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-nicotinamide

20 This material was prepared as for Example 3 except that 6-morpholin-4-nicotinic acid was used. The title compound was a colourless solid (28mg).

¹H NMR (DMSO, d) 3.58-3.61 (m, 4H) 3.70-3.73 (m, 4H) 5.51 (d, 1H) 6.89 (d, 1H) 7.24-7.71 (m, 9H) 8.19 (dd, 1H) 8.80 (d, 1H) 9.39 (d, 1H) 10.89 (s, 1H)
RT= 4.59mins, ES+ 442

25

Example 48

(S)-3-Morpholin-4-ylmethyl-thiophene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

30

This material was prepared as for Example 3 except that 3-morpholin-4-ylmethyl-thiophene-2-carboxylic acid (Intermediate 29) was used. The title compound was a

colourless solid (34mg).

¹H NMR (DMSO, d) 2.43 (m, 4H) 3.59 (m, 4H) 3.70 (s, 2H) 5.45 (d, 1H) 7.05 (d, 1H) 7.24-7.70 (m, 9H) 8.05 (d, 1H) 9.54 (d, 1H) 10.92 (s, 1H)

5 RT= 5.02mins, ES+ 461

Example 49

10 (S)-5-Morpholin-4-ylmethyl-thiophene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

This material was prepared as for Example 3 except that 5-morpholin-4-ylmethyl-thiophene-2-carboxylic acid (Intermediate 30) was used. The title compound was a colourless solid (41mg).

15

¹H NMR (DMSO, d) 2.28 (brm, 4H) 3.38 (brm, 4H) 3.56 (s, 2H) 5.16 (d, 1H) 6.90 (d, 1H) 7.04-7.44 (m, 9H) 7.52 (d, 1H) 10.68 (s, 1H) 11.82 (d, 1H)

RT= 5.33mins, ES+ 461

20 Example 50

2-Morpholin-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide

25 This material was prepared as for Intermediate 15 except that 2-morpholin-4-yl-benzoic acid (49mg) was used. The product was a colourless solid (33mg)

¹H NMR (DMSO, d) 3.01-3.12 (m, 4H) 3.86-3.93 (m, 4H) 5.44 (d, 1H) 7.21-7.71 (m, 12H) 7.93 (dd, 1H) 10.99 (d, 1H) 11.02 (s, 1H)

30 RT=5.47, ES+441

Example 51

(S)- 5-Phenyl-oxazole-4-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide

- 5 (S)-3-Amino-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one (60mg), triethylamine (0.037ml) and 5-phenyl-oxazole-4-carbonyl chloride (50mg) in THF (3ml) were stirred at room temperature for 2h. The mixture was then partitioned between water and dichloromethane. The dried organic phase was evaporated and the residue purified on a silica gel SPE cartridge. Elution with
- 10 dichloromethane:ethanol:0.880 ammonia; 400:8:1 gave the title compound as a colourless solid (42mg).

¹H NMR (DMSO, \square) 5.40 (d, 1H) 7.27-7.70 (m, 12H) 8.22-8.26 (m, 2H) 8.72 (s, 1H) 8.88 (d, 1H) 11.14 (s, 1H)

15 RT=5.22, ES+423.49

Example 52

20 1-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-(4-phenoxy-phenyl)-urea

- Racemic 3-Amino-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one (30mg) and 1-isocyanato-4-phenoxy-benzene (0.022ml) in dry THF (4ml) was stirred at room temperature for 18h. The mixture was then partitioned between water and
- 25 dichloromethane. The dried organic layer was evaporated and the residue triturated from dichloromethane/diethyl ether giving the title compound as a white solid (25mg)

1H NMR (DMSO, d) 5.23 (d, 1H) 6.98-7.03 (m, 3H) 7.11 (t, 1H) 7.33-7.58 (m, 13H)

30 7.71 (dt, 1H) 9.18 (s, 1H) 11.03 (brs, 1H)

RT=5.57, ES+463.45

ACTIVITY EXAMPLE 1

XTT Assay Protocol

- 5 The inner 60 wells of 96 well tissue culture plates were seeded with Hep-2 cells at 4×10^4 cells/well for compound activity and toxicity studies in 100 μ l of medium and incubated at 37°C overnight or until nearing confluency.

- 10 Cells were infected with 25 μ l RSV previously titrated to give 80% cell kill. To each well 25 μ M of test compound were added. The final DMSO concentration was 0.5%. Some 200 μ l of sterile distilled water were added to the outer wells of the plate and incubated at 37°C for 6 days. Some 0.25 μ l/ml PMS were added to stock XTT solution, final conc. 25 μ M PMS. Then 25 μ l warmed XTT/PMS solution were added to each well and incubated for 1 hour at 37°C.

- 15 Maximum OD_{450nm} reading (uninfected, untreated control cells) corresponded to 100% inhibition. Minimum OD_{450nm} readings (infected control cells) corresponded to 0% inhibition. Log10 concentration was plotted against OD_{450nm} and IC₅₀ values were calculated from either reading 50% value from graph or using regression
- 20 analysis.

Patent Example Number	IC ₅₀ (\square M)	TD ₅₀ (\square M)
1	5.7	>50
2	5.4	>50
3	1.5	>50
4	1.5	25
5	4.9	>50
6	1.4	50
7	1.2	>50

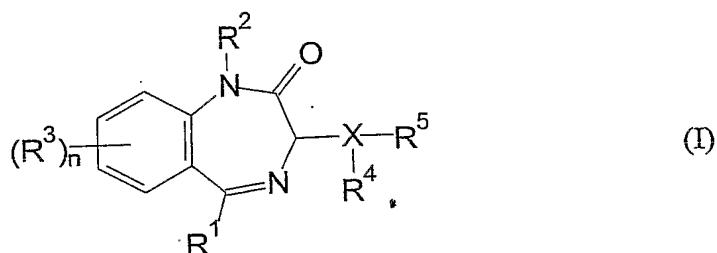
Patent Example Number	IC ₅₀ (\square M)	TD ₅₀ (\square M)
27	9.3	>50
28	9.6	>50
29	2.7	>50
30	5.9	>50
31	4.7	>50
32	3	>50
33	2.8	>50

8	5.3	>50
9	4.9	>50
10	4.2	>50
11	5.1	>50
12	7.6	12.5
13	2.9	50
14	10.5	25
15	5.7	12.5
16	5.2	12.5
17	2.4	6.25
18	4.8	25
19	23.3	>50
20	5.1	25
21	4.3	>50
22	3	>50
23	10.1	>50
24	1	>50
25	18	>50
26	10.9	>50

34	4.8	>50
35	2.2	>50
36	4.5	>50
37	9.1	>50
38	1.4	>50
39	2	>50
40	4.4	>50
41	5.7	>50
42	2.6	>50
43	8.6	>50
44	4.8	>50
45	2.6	>50
46	3.9	>50
47	2.1	>50
48	2.3	>50
49	7.7	>25
50	2	100
51	0.62	>50
52	1.5	>100

CLAIMS

1. Use of a compound which is (a) a benzodiazepine derivative of the formula
(I) or an N-oxide thereof or (b) a pharmaceutically acceptable salt thereof, in the
5 manufacture of a medicament for use in treating or preventing an RSV infection

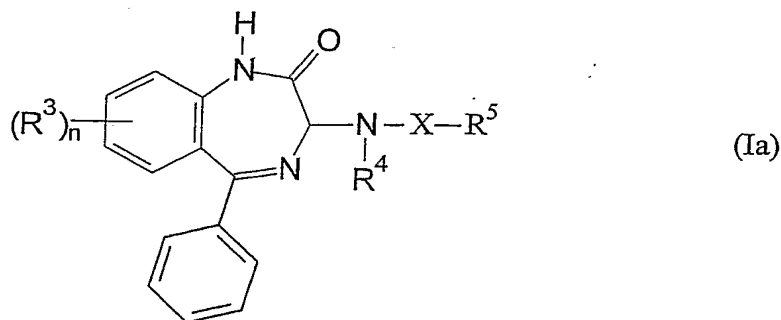


wherein:

- R^1 represents C_{1-6} alkyl, aryl or heteroaryl;
- 10 - R^2 represents hydrogen or C_{1-6} alkyl;
- each R^3 is the same or different and represents halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} haloalkyl, C_{1-6} haloalkoxy, amino, mono(C_{1-6} alkyl)amino, di(C_{1-6} alkyl)amino, nitro, cyano, $-CO_2R'$, $-CONR'R''$, $-NH-CO-R'$, $-S(O)R'$, $-S(O)_2R'$, $-NH-S(O)_2R'$, $-S(O)NR'R''$ or $-S(O)_2NR'R''$, wherein each R' and
- 15 R'' is the same or different and represents hydrogen or C_{1-6} alkyl;
- n is from 0 to 3;
- R^4 represents hydrogen or C_{1-6} alkyl;
- X represents $-CO-$, $-CO-NR'-$, $-S(O)-$ or $-S(O)_2-$, wherein R' is hydrogen or a C_1-C_6 alkyl group; and
- 20 - R^5 represents an aryl, heteroaryl or heterocyclyl group, which group is substituted by a C_1-C_6 hydroxyalkyl group or a $-(C_1-C_4 \text{ alkyl})-X_1-(C_1-C_4 \text{ alkyl})-X_2-$ (C_1-C_4 alkyl) group, wherein X_1 represents $-O-$, $-S-$ or $-NR'-$, wherein R' represents H or a C_1-C_4 alkyl group and X_2 represents $-CO-$, $-SO-$ or $-SO_2-$, or R^5 represents $-A_1-Y-A_2$, wherein:
- 25 - A_1 is an aryl, heteroaryl, carbocyclyl or heterocyclyl group;
- Y represents a direct bond or a C_1-C_4 alkylene, $-SO_2-$, $-CO-$, $-O-$, $-S-$ or $-NR'-$ moiety, wherein R' is a C_1-C_6 alkyl group; and

- A₂ is an aryl, heteroaryl, carbocyclyl or heterocyclyl group.
- 2. Use according to claim 1, wherein R¹ is C₁₋₂ alkyl or phenyl.
- 3. Use according to claim 1 or 2, wherein R² is hydrogen.
- 5 4. Use according to any one of the preceding claims wherein R³ is halogen, hydroxy, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ haloalkyl, C₁₋₄ haloalkoxy, amino, mono(C₁₋₄ alkyl)amino or di(C₁₋₄ alkyl)amino.
- 10 5. Use according to claim 4, wherein R³ is fluorine, chlorine, bromine, C₁₋₂ alkyl, C₁₋₂ alkoxy, C₁₋₂ alkylthio, C₁₋₂ haloalkyl, C₁₋₂ haloalkoxy, amino, mono(C₁₋₂ alkyl)amino or di (C₁₋₂ alkyl)amino.
- 15 6. Use according to any one of the preceding claims wherein R⁴ is hydrogen or C₁₋₂ alkyl.
- 7. Use according to any one of the preceding claims wherein X is -CO- or -CO-NR' wherein R' represents hydrogen or a C₁₋₂ alkyl group.
- 20 8. Use according to any one of the preceding claims, wherein R⁵ is a 5- or 6-membered heterocyclyl or heteroaryl ring which is substituted by a C₁₋₆ hydroxyalkyl group or a -(C₁₋₄ alkyl)-X₁-(C₁₋₄ alkyl)-X₂-(C₁₋₄ alkyl) group, wherein X₁ and X₂ are as defined in claim 1.
- 25 9. Use according to claim 8, wherein R⁵ is a 5- or 6- membered heteroaryl group which is substituted by a -CH₂-OH or -(C₁₋₄ alkyl)-NR'-(C₁₋₄ alkyl)-S(O)₂-(C₁₋₄ alkyl) substituent, wherein R' is hydrogen or C₁₋₂ alkyl.
- 30 10. Use according to any one of the preceding claims, wherein A₁ is an aryl or heteroaryl group.

11. Use according to claim 10, wherein A₁ is a phenyl group, a monocyclic 5- or 6- membered heteroaryl group or a 5- to 6- membered heteroaryl group fused to a monocyclic oxo-substituted 5- to 6- membered heterocyclyl group.
- 5 12. Use according to any one of the preceding claims wherein A₁ is unsubstituted or substituted by 1 or 2 substituents selected from halogen, cyano, nitro, C₁-C₄ alkyl, C₁-C₄ haloalkyl and C₁-C₄ alkoxy substituents.
- 10 13. Use according to any one of the preceding claims, wherein Y represents a direct bond, a C₁-C₂ alkylene group, -SO₂- or -O-.
14. Use according to any one of the preceding claims, wherein A₂ is a phenyl, 5- to 6- membered heteroaryl, 5- to 6- membered heterocyclyl or C₃-C₆ cycloalkyl group.
- 15 15. Use according to any one of the preceding claims, wherein when A₂ is a heterocyclyl group it is attached to the moiety Y via a N atom.
- 20 16. Use according to any one of the preceding claims, wherein A₂ is unsubstituted or is substituted by 1 or 2 substituents which are selected from C₁-C₄ alkyl and halogen substituents when A₂ is a heteroaryl or aryl group and which are selected from C₁-C₄ alkyl, halogen and oxo substituents when A₂ is a carbocyclic or heterocyclyl group.
- 25 17. Use according to any one of the preceding claims, wherein A₂ is a piperazinyl, pyridyl, morpholinyl, pyrrolidinyl, piperidinyl, pyrazinyl, cyclopropyl, phenyl or S,S-dioxo-thiomorpholino group, which is unsubstituted or substituted by a C₁-C₂ alkyl group.
- 30 18. Use according to any one of the preceding claims wherein the benzodiazepine derivative of formula (I) is a benzodiazepine derivative of formula (Ia):



wherein:

- X is -CO- or -CO-NH-; and
- 5 - R^5 is a 5- to 6- membered heteroaryl group, for example a furanyl group, which is substituted by -CH₂-OH or -(C₁-C₄ alkyl)-N(CH₃)-(C₁-C₄ alkyl)-SO₂-(C₁-C₄ alkyl) or R_5 represents -A₁-Y-A₂, wherein:
 - A₁ is a phenyl, pyridyl, furanyl, thiazolyl, oxazolyl, isoxazolyl, thienyl or 1H-imidazo[4,5-b]pyridin-2-(3H)-one moiety, which is unsubstituted or substituted
 - 10 by 1 or 2 substituents selected from halogen, cyano, C₁-C₂ alkyl, C₁-C₂ haloalkyl and C₁-C₂ alkoxy substituents;
 - Y is a direct bond, a C₁-C₂ alkylene group, -SO₂- or -O-; and
 - A₂ is a piperazinyl, pyridyl, morpholinyl, pyrrolidinyl, piperidinyl, pyrazinyl, cyclopropyl, phenyl or S,S-dioxo-thiomorpholino group, which is unsubstituted or
 - 15 substituted by a C₁-C₂ alkyl group.
- 19. Use according to any one of the preceding claims, wherein the medicament is for use in treating a patient who is a child under two years of age, an adult suffering from asthma, chronic obstructive pulmonary disorder (COPD) or immunodeficiency,
- 20 an elderly person or a person in a long term care facility.
- 20. Use according to claim 19 wherein said child suffers from chronic lung disease.
- 25 21. Use according to any one of claims 1 to 18 wherein the medicament is for use in preventing RSV infection in an infant less than six years of age who was born after 32 weeks of gestation or less.

22. Use according to any one of the preceding claims, wherein the medicament is suitable for intranasal or intrabronchial administration.
- 5 23. Use according to any one of the preceding claims, wherein the medicament further comprises an anti-inflammatory compound or an anti-influenza compound.
24. Use according to claim 23 wherein the anti-inflammatory compound is budesonide or fluticasone.
- 10 25. Use according to claim 23 wherein the anti-inflammatory compound is a leukotriene antagonist, phosphodiesterase 4 inhibitor or TNF alpha inhibitor.
- 15 26. Use according to claim 23 wherein the anti-inflammatory compound is an interleukin 8 or interleukin 9 inhibitor.
27. Use according to any one of claims 1 to 22 wherein the medicament is coadministered with an anti-inflammatory compound, as defined in any one of claims 24 to 26, or an anti-influenza compound.
- 20 28. A method of treating a patient suffering from or susceptible to an RSV infection, which method comprises administering to said patient an effective amount of a compound as defined in any one of claims 1 to 18.
- 25 29. A method according to claim 28, wherein said patient is a patient as defined in any one of claims 19 to 21.
30. A method according to claim 28 or 29, wherein said compound is administered intranasally or intrabronchially.
- 30 31. An inhaler or nebuliser containing a medicament which comprises
- (a) a compound as defined in any one of claims 1 to 18, and

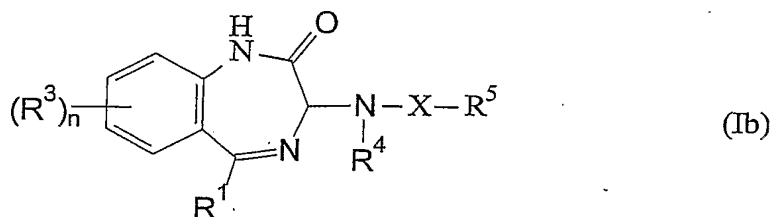
(b) a pharmaceutically acceptable carrier or diluent.

32. A product comprising a compound as defined in any one of claims 1 to 18 and an anti-inflammatory compound, as defined in any one of claims 24 to 26, or an anti-influenza compound.

33. Use of a product according to claim 32 in the manufacture of a medicament for use in the treatment of concomitant RSV and influenza infections.

34. Use of a compound as defined in any one of claims 1 to 18 in the manufacture of a medicament for use in the treatment of human metapneumovirus, measles, parainfluenza viruses, mumps, yellow fever virus (B5 strain), Dengue 2 virus or West Nile virus.

35. A compound which is (a) a benzodiazepine derivative of formula (Ib) or an N-oxide thereof, or (b) a pharmaceutically acceptable salt thereof



wherein R_1 , R_3 , n , R_4 , X and R_5 are as defined in any one of claims 1 to 18.

36. A compound according to claim 35, wherein R_1 is an unsubstituted phenyl group.

37. A compound according to claim 35 or 36, wherein when A_1 is a heteroaryl group, it is other than a 5-methyl-isoxazolyl moiety.

38. A compound according to any one of claims 35 to 37, wherein A_1 is an aryl or heteroaryl moiety.

39. A compound according to any one of claims 35 to 38, wherein X is -CO- or -CO-NR', wherein R' is as defined in any one of claims 1 to 18; provided that when X is -CO-NR', the moiety -A₁-Y-A₂ is -phenyl-O-phenyl.

5

40. A compound according to any one of claims 35 to 39, wherein A₂ is other than a 4- to 10- membered saturated cycloalkyl ring, in which one of the carbon atoms is replaced by a N atom.

10 41. A compound according to any one of claims 35 to 40, wherein A₂ is a piperazinyl, pyridyl, pyrrolidinyl, pyrazinyl, cyclopropyl, phenyl or S,S-dioxo-thiomorpholino group which is unsubstituted or is substituted by a C₁-C₂ alkyl group.

15 42. A compound according to claim 35, wherein the benzodiazepine derivative of the formula (Ib) is:

6-(4-Methyl-piperazin-1-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-nicotinamide;

3,4,5,6-Tetrahydro-2H-[1,2']bipyridinyl-5'-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

20 (S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

(S)-2-Chloro-4-morpholin-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

25 (S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-4-fluoro-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

(S)-5-Chloro-2-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

(S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-5-fluoro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;

30 (S)-5-(4-Methyl-piperazin-1-ylmethyl)-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;

(S)-5-Pyrrolidin-1-ylmethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-

- 1H-benzo[e][1,4]diazepin-3-yl)-amide;
 (S)-5-Piperidin-1-ylmethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 (S)-5-Dimethylaminomethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 5 (S)-4-Fluoro-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-piperidin-1-yl-benzamide;
 (S)-4-Fluoro-2-morpholino-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
 10 (S)-4-Cyano-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-pyrrolidin-1-yl-benzamide;
 (S)-4-Cyano-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-piperidine-1-yl-benzamide;
 (S)-N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-pyrrolidin-1-yl-4-trifluoromethyl-benzamide;
 15 (S)-N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-piperidin-1-yl-4-trifluoromethyl-benzamide;
 (S)-2-Morpholin-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-4-trifluoromethyl-benzamide;
 20 (S)-N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-2-pyrrolidin-1-yl-5-trifluoromethyl-benzamide;
 (S)-2-Morpholin-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-5-trifluoromethyl-benzamide;
 (S)-2-Morpholin-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-nicotinamide;
 25 (S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-nicotinamide;
 (S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-3-methyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
 30 (S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-4-methyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
 (S)-2-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-6-methyl-N-(2-oxo-5-phenyl-2,3-

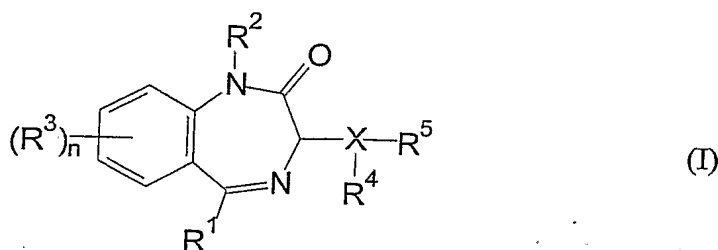
- dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
 (S)-2-Chloro-6-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
 (S)-3-Cyclopropyl-2-oxo-2,3-dihydro-imidazo[4,5-b]pyridine-1-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 5 (S)-3-(4-Methyl-piperazine-1-sulfonyl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
 (S)-4-(4-Methyl-piperazin-1-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
 10 (S)-N-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-(piperidine-1-sulfonyl)-benzamide;
 (S)-3-(Morpholine-4-sulfonyl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
 (S)-5-Morpholin-4-ylmethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 15 (S)-5-Hydroxymethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 (S)-5-(1,1-Dioxo-1λ6-thiomorpholin-4-ylmethyl)-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 20 (S)-2-Chloro-4-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
 (S)-2-Chloro-5-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-benzamide;
 (S)-5-([(2-Methanesulfonyl-ethyl)-methyl-amino]-methyl)-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 25 (S)-2-Pyridin-3-yl-thiazole-4-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 (S)-2-Pyridin-4-yl-thiazole-4-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 30 (S)-4-Methyl-2-pyrazin-2-yl-thiazole-5-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 (S)-2-Morpholin-4-ylmethyl-furan-3-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-

- 1H-benzo[e][1,4]diazepin-3-yl)-amide;
 (S)-3-Morpholin-4-ylmethyl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]
 diazepin-3-yl)-benzamide;
 (S)-5-Morpholin-4-ylmethyl-isoxazole-3-carboxylic acid (2-oxo-5-phenyl-2,3-
 5 dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 (S)-3-Morpholin-4-ylmethyl-furan-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-
 1H-benzo[e][1,4]diazepin-3-yl)-amide;
 (S)-5-Pyridin-2-yl-thiophene-2-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-
 benzo[e][1,4]diazepin-3-yl)-amide;
 10 (S)-2-Methyl-4-(morpholin-4-sulfonyl)-furan-3-carboxylic acid (2-oxo-5-phenyl-2,3-
 dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 (S)-6-Morpholin-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-
 yl)-nicotinamide;
 (S)-3-Morpholin-4-ylmethyl-thiophene-2-carboxylic acid (2-oxo-5-phenyl-2,3-
 15 dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 (S)-5-Morpholin-4-ylmethyl-thiophene-2-carboxylic acid (2-oxo-5-phenyl-2,3-
 dihydro-1H-benzo[e][1,4]diazepin-3-yl)-amide;
 2-Morpholin-4-yl-N-(2-oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-
 benzamide;
 20 (S)-5-Phenyl-oxazole-4-carboxylic acid (2-oxo-5-phenyl-2,3-dihydro-1H-
 benzo[e][1,4]diazepin-3-yl)-amide; or
 1-(2-Oxo-5-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-3-yl)-3-(4-phenoxy-
 phenyl)-urea.
- 25 43. A compound according to any one of claims 35 to 42 for use in a method of
 treating the human or animal body.
44. A pharmaceutical composition comprising a compound according to any one
 of claims 35 to 43, and a pharmaceutically acceptable diluant or carrier.
- 30 45. A composition according to claim 44 comprising an optically active isomer of
 a compound according to any one of claims 35 to 42.

46. A composition according to claim 44 or 45 which is in the form of a tablet, troche, lozenge, aqueous or oily suspension, dispersible powders or granules.

ABSTRACT
CHEMICAL COMPOUNDS

Use of a compound which is (a) a benzodiazepine derivative of the formula
5 (I) or an N-oxide thereof or (b) a pharmaceutically acceptable salt thereof, in the
manufacture of a medicament for use in treating or preventing an RSV infection



wherein:

- R¹ represents C₁₋₆ alkyl, aryl or heteroaryl;
- 10 - R² represents hydrogen or C₁₋₆ alkyl;
- each R³ is the same or different and represents halogen, hydroxy, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio, C₁₋₆ haloalkyl, C₁₋₆ haloalkoxy, amino, mono(C₁₋₆ alkyl)amino, di(C₁₋₆ alkyl)amino, nitro, cyano, -CO₂R', -CONR'R'', -NH-CO-R', -S(O)R', -S(O)₂R', -NH-S(O)₂R', -S(O)NR'R'' or -S(O)₂NR'R'', wherein each R' and
- 15 R'' is the same or different and represents hydrogen or C₁₋₆ alkyl;
- n is from 0 to 3;
- R⁴ represents hydrogen or C₁₋₆ alkyl;
- X represents -CO-, -CO-NR', -S(O)- or -S(O)₂-, wherein R' is hydrogen or a C₁₋₆ alkyl group; and
- 20 - R⁵ represents a heteroaryl or heterocyclyl group which is substituted by a C₁₋₆ hydroxyalkyl group or a -(C₁₋₄ alkyl)-X₁-(C₁₋₄ alkyl)-X₂-(C₁₋₄ alkyl) group, wherein X₁ represents -O-, -S- or -NR', wherein R' represents H or a C₁₋₄ alkyl group and X₂ represents -CO-, -SO- or -SO₂-, or R₅ represents -A₁-Y-A₂, wherein:
 - A₁ is an aryl, heteroaryl, carbocyclyl or heterocyclyl group;
 - 25 - Y represents a direct bond or a C₁₋₄ alkylene, -SO₂-, -CO-, -O-, -S- or -NR' moiety, wherein R' is a C₁₋₆ alkyl group; and
 - A₂ is an aryl, heteroaryl, carbocyclyl or heterocyclyl group.

